MDMA-ASSISTED THERAPY FOR POST-TRAUMATIC STRESS DISORDER: PHASE 2 EVIDENCE SYNTHESIS

A REPORT TO THE UTAH PSYCHOTHERAPY DRUG TASK FORCE

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ABBREVIATIONS

AE	Adverse event
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
CI	Confidence interval
CAPS	Clinician-administered PTSD Scale; CAPS-5 is for the Diagnostic and Statistical Manual of Mental Disorders (DSM) version V, and CAPS-4 is for DSM version IV
CSSRS	Columbia Suicide Severity Rating Scale
CRP	C-reactive protein
DEA	U.S. Drug Enforcement Agency
DUDIT	Drug Use Disorders Identification Test
FDA	U.S. Food and Drug Administration
ITT	Intention to treat
LSD	(D)-Lysergic acid diethylamide
MDD	Major depressive disorder
MDMA	3,4-methylenedioxymethamphetamine
NCT	National Clinical Trial
PTGI	Posttraumatic Growth Inventory
PTSD	Post-traumatic stress disorder
RCT	Randomized controlled trial
ROB	Risk of bias
SAE	Serious adverse event
SD	Standard deviation
SDS	Sheehan Disability Scale
SR	Systematic review
SUD	Substance use disorder
TEAE	Treatment-emergent adverse event
TFP	Trauma-focused psychotherapy

1.0 INTRODUCTION

Post-traumatic stress disorder (PTSD) is characterized by persistent re-experience of intrusive memories, avoidance behaviors, negative changes in mood or cognition, and heightened arousal, all occurring after exposure to a traumatic event.[1] Examples of initial traumatic events include exposure to abuse, war, other violence, or accidents.[1] Neuroscience research suggests that PTSD develops from a dysregulation of the fear response that is commonly associated with neuroanatomical changes including increased amygdala activation with decreased hippocampal and prefrontal cortex activation.[2]

An estimated 6-8% of people in the United States (US) develop PTSD during their lifetime[1]; 2 groups with high affected proportions include women and people who have served in the military.[1,3] PTSD is associated with impaired psychosocial functioning,[4,5] high rates of psychological (eg, mood or substance use disorders)[4] and medical comorbidities,[6] and higher all-cause mortality relative to the general US population.[7] One estimate found that approximately two-thirds of surveyed US adults with PTSD experienced moderate to serious impairment over a 12-month period.[8] The estimated US societal burden from PTSD exceeds 200 billion per year, based upon the total excess costs compared to the general US adult population without PTSD.[7]

PTSD is typically treated with psychotherapeutic or pharmacotherapeutic approaches.[9-11] Recent US clinical practice guidelines (CPGs) give their highest recommendations to trauma-focused psychotherapies (TFPs) as a first-line treatment,[12] these therapies involve direct exposure to memories or feelings of the triggering event. TFP approaches are typically conducted over about 12 sessions using a manualized protocol.[13] Based on recent brain imaging evidence from PTSD-affected individuals undergoing a type of TFP, prolonged exposure (PE), TFP may work by helping to rewire aberrant connectivity between the frontoparietal and limbic regions of the brain.[14] Examples of TFP recommended by both the 2017 CPG from the Department of Veteran's Affairs (VA)/Department of Defense (DoD) and American Psychological Association (APA) are cognitive therapy, cognitive behavioral therapy, and PE.[9,10]

Non-trauma-focused psychotherapy and pharmacotherapy with certain selective serotonin or serotonin and norepinephrine reuptake inhibitors (SSRIs or SNRIs) are also recommended options by CPGs.[9,10] These modalities are important because TFP may be inaccessible, intolerable, or not preferred by many PTSD suffers.[9] The only FDA-approved drug therapies for PTSD are the SSRIs, sertraline and paroxetine (immediate-release).[15,16] Compared to TFP, these treatments may be less effective and produce shorter-lasting benefits, based only on indirect comparison of treatment effect sizes.[17]

These current evidence-based treatment approaches for PTSD are limited by tolerability (based on high dropout rates during clinical trials) and efficacy.[13,17,18] An estimated 20-50% of people do not adequately respond to either TFP or non-trauma-focused psychotherapy and pharmacotherapy.[19]

The nonprofit organization, Multidisciplinary Association for Psychedelic Studies (MAPS), is pursuing U.S. Food and Drug Administration (FDA) approval of 3,4-methylenedioxymethamphetamine (MDMA)[*] for

[***] *The generic name 'midomafetamine' or 'midomafetamine hydrochloride' are also terms for MDMA. We use MDMA in this report.*

treatment of PTSD in combination with nondirective psychotherapy (often referred to as MDMA-assisted therapy). In 2017, the FDA issued the Breakthrough Therapy Designation to MAPS-sponsored MDMA for the treatment of PTSD following positive results from a pooled assessment of phase 2 studies.[20,21] This designation, for drugs showing promise to treat a serious illnesses, creates a smoother pathway to future FDA approval by assisting sponsors with trial study design and expedited evidence review.[22] MAPS plans to submit its FDA approval application in 2023 after the completion of its second phase 3 clinical trial, which is anticipated in late 2022.[23] If sufficient safety and efficacy evidence is observed FDA approval could be granted within 24 months of May 2022.[24]

MDMA belongs to the drug class entactogens (or empathogens).[25,26] The mechanism of action is not fully understood; the molecules are structurally similar to amphetamines, but their effects are distinct from those of psychostimulants.[25] Pharmacologic research findings suggest the entactogens may stimulate release of serotonin and norepinephrine.[25] MDMA also has an affinity for the dopamine transporter, but at a much lower potency compared to (S)-amphetamine.[27] It may also trigger dopaminergic release (via its effect on serotonin).[28] In addition to stimulating monoamine release by various mechanisms, MDMA also has affinities for other neuroreceptors (eg, adrenergic, histaminergic, muscarinic), and it increases various hormone levels including cortisol, prolactin, vasopressin, oxytocin, and dehydroepiandrosterone.[27]

Behavioral effects of MDMA in healthy volunteers include increased feelings of trust and empathy, and increased "prosocial" activity (eg, minimization of differences between two individuals).[28,29] Additionally, in healthy volunteers, MDMA increased subjective ratings of favorable memories, and decreased subjective ratings of individual's worst memories compared to placebo.[30] Cumulatively these observations led to the application of MDMA as a catalyst for increasing the effectiveness of psychotherapy.[31] For example, MDMA *may* facilitate a stronger alliance with therapists and easier processing of traumatic memories.[32]

The proposed MDMA formulation for marketing is the salt (hydrochloride [HCl]) of *racemic* MDMA[†]. At a fixed oral single dose of 1-4 mg/kg, this formulation had an onset of effect and the peak effect at 30-60 minutes and 75 to 120 minutes, respectively after a single dose, and an estimated effect duration of about 6 hours. The elimination half-life is approximately 7 to 9 hours, with metabolites excreted in the urine. Because MDMA is applied as a psychotherapy catalyst (ie, administered only intermittently during psychotherapy), steady-state MDMA concentrations were not examined.[31] In PTSD clinical trials, MDMA was administered in divided doses for 2-3 sessions, each separated by approximately 3-5 weeks.[32,33]

The **goal of this report** is to summarize efficacy and safety information from published or unpublished randomized controlled trials (RCTs) of MDMA-assisted therapy for the treatment of PTSD and assesses the risk of bias (ROB) in the trials. Together this information will assist the Utah "Mental Illness Psychotherapy Drug Task Force" (referred to as "Task Force") in meeting their assigned duties established by Utah H.B. 167.[34] This report was informed by a preliminary search and annotated

[†] *MAPS reports using standardized batches of MDMA HCl made according to good clinical manufacturing practices in MAPS-sponsored studies since November 2018. These are formulated as 40 or 60 mg capsules (corresponding to 34 and 50 mg of MDMA, respectively) with inactive ingredients of mannitol, magnesium stearate, and hydroxypropylmethylcellulose with good stability at 25°C in aluminum blister packs for at least 36 months, or for at least 24 months in plastic bottles (stability studies under different conditions are ongoing).*

bibliography of studies for 5 psychotherapy drugs including MDMA (ie, Phase I of this project)[35]; please refer to the Phase I Report for additional background information: https://www.utah.gov/pmn/files/868105.pdf.

2.0 METHODS

This report was preceded by a preliminary report (Phase I Report) that included a search of 2 major bibliographic databases (Embase and Ovid-Medline) and ClinicalTrials.gov for experimental trials or long-term follow-up of experimental trials for 5 psychotherapy drugs: MDMA, lysergic acid diethylamide (LSD), psilocybin, ayahuasca, and ibogaine. The bibliographic database searches were completed June 2, 2022, and the ClinicalTrials.gov search for MDMA was completed May 4, 2022. Included studies were summarized as an annotated bibliography and delivered to the Task Force on June 30, 2022.[35] Refer to the phase I report for additional details: https://www.utah.gov/pmn/files/868105.pdf. **Table 1** contains a summary of the activities in the various phases of this project.

Table 1. Overview of Psychotherapy Drug[a] Evidence Review Phases

Phase	Description	Primary Deliverable(s)	Status
I	Literature search for RCTs in Medline and Embase • Addressed 5 psychotherapy drugs (MDMA, LSD, Psilocybin, Ayahuasca, Ibogaine) for targeted mental health conditions	• Annotated bibliography • Summary of registered trials on ClinicalTrials.gov	Completed[b]
II	RCT evidence synthesis with supplemental searching of additional bibliographic databases including PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL) • Focus on 2 drug-disease pairs: MDMA for PTSD, and psilocybin for depression	• Summary of RCT efficacy and safety evidence per drug and indication. • Evaluation of the ROB among RCT evidence	MDMA for PTSD: completed Psilocybin for depression: in-progress
III	To be completed if needed to address questions insufficiently addressed by phase II		As needed

Abbreviations: LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; ROB, risk of bias

[a] 'Psychotherapy drug' is a term used by Utah H.B. 167 to refer to controlled substances that might be effective for treating mental illness[34] such as MDMA or psilocybin

[b] https://www.utah.gov/pmn/files/868105.pdf

Based on the Phase I literature search, it was determined that the majority of published phase 2 or phase 3 randomized, controlled trial (RCT) evidence was for 2 evaluated drug-disease pairs: MDMA for PTSD (5 trials) and psilocybin for major depressive disorder (3 trials).[35] Due to the large volume of evidence included in the Phase I report and the October deadline for the Task Force to advise the Utah legislature on its findings, we agreed to narrow the focus for Phase II of the evidence review. At the July 12, 2022 Task Force meeting, we agreed to focus on 2 drug-disease pairs (MDMA for PTSD and psilocybin for depression), which are furthest along in clinical development based on completed RCTs, and thus present the greatest opportunity for the Task Force to advise on their potential use in Utah.

This report focuses on MDMA-assisted therapy for treatment of PTSD. RCT evidence of psilocybin's use in depression will be summarized in a separate report. These evidence synthesis reports can be classified as 'rapid reviews' with a qualitative evidence synthesis of RCT evidence and risk of bias (ROB) assessment. (Upon completion of the qualitative syntheses, we will make recommendations about whether a quantitative synthesis is warranted). We refer to these evidence synthesis reports collectively as Phase II of our work; it includes an expanded literature search of 2 additional major bibliographic databases: PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL), with supplemented searches from Phase I of the project.

A protocol for Phase II of the evidence review was drafted and submitted to Task Force leaders on July 27, 2022. Two deviations from this protocol occurred due to feasibility constraints: (1) the approach for the risk of bias assessment was changed, and (2) the breadth of detail about the psychotherapy approach, setting, and safety monitoring was restricted. For the ROB assessment, we originally planned to use the Cochrane Collaboration Risk of Bias 2 tool, but this was changed to the domain-based approach recommended by Page et al, which includes an abbreviated approach to assessing all of the major sources of bias included in the Cochrane tool.[36] Extraction of additional details about the setting, conduct and safety monitoring was restricted to only the phase 3 trial (rather than all included trials). The rationale for the latter change was that all of the trials had the same sponsor, and thus the phase 2 trials established the methods for the set the phase 3 studies' design.

2.1 Bibliographic Database Search and Screening of Records

Four major bibliographic databases (Ovid-Medline, Embase, PsycINFO, and CENTRAL) were queried for relevant evidence published from 2010 to the date of the search (June 3, 2022 for Ovid-Medline and Embase, and July 19, 2022 for PsycINFO and CENTRAL). The publication date restriction was selected based on feasibility and consultation with content experts. An initial search using free-text and controlled vocabulary terms (ie, MeSH) for MDMA and PTSD concepts that included synonyms and/or different spellings for each concept was developed in Ovid-Medline and translated to the other databases. Multiple investigators with expertise in conducting literature searches developed and peer-reviewed each literature search. Validated hedges for randomized controlled trials (RCTs) were used for the searches in Ovid-Medline (a sensitivity- and precision-maximized version from The Cochrane Collaboration modified to include "randomised" spelling),[37] and Embase.[38] A validated hedge for Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost was adapted to PsycINFO-EBSCOhost.[39] The CENTRAL (ie, Cochrane Central Register of Controlled Trials) database pulls published and unpublished records and trial registry information from multiple sources including bibliographic databases (ie, PubMed, Embase, CINAHL), and national and international registries (ie, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform).[40] Refer to **Appendix A** for the search strategies used in PsycINFO and CENTRAL. Searches in Embase and Ovid-Medline are accessible in our phase I report.

Bibliographic database searches were supplemented by screening reference lists of included studies for additional eligible studies. In addition, for each included registered trial, ClinicalTrials.gov was searched for additional information/results for included studies (eg, trial protocol and results reported in the database). The MDMA-assisted therapy sponsor's website (https://maps.org/) was also searched for supporting information about use of MDMA; the most recent MAPS Investigator's Brochure and relevant press releases were referenced, and RCTs reported in the Investigator's Brochure were

reviewed for possible inclusion. When applicable, additional subject were retrieved as identified from published text (eg, protocol for MAPS-assisted therapy).

Title and abstract screening of search results from bibliographic databases were screened independently and in duplicate using the review software Covidence. Disagreements were resolved by consensus. Articles pushed to full-text review based on the results of the title and abstract were assessed for eligibility by a single author who consulted with additional authors as needed. MDMA studies included in the phase I annotated bibliography were reviewed by two authors to confirm whether they met the stricter eligibility criteria used in the phase II evidence review.

2.2 Eligibility Criteria for Inclusion in the Qualitative Evidence Synthesis

Studies meeting the following criteria were included for this phase II report on MDMA:

- Study designs included individual experimental trials (ie, RCTs). We also considered summary studies (ie, including 2 or more RCTs) conducted by the sponsors of MDMA-assisted therapy RCTs that reported findings not found in individual trial reports.
    - We included comparisons of MDMA versus controls in either a parallel or crossover study design; for crossover designs with persistent treatment effects, we only reported on comparisons that preceded the crossover.
- Population was participants diagnosed with PTSD.
    - For studies including a heterogeneous population of people with PTSD with or without other diagnosed mental health conditions, we only included studies reporting comparisons among people in the PTSD subpopulation only.
- Intervention was MDMA at any dose, duration, or formulation.
    - MDMA could be combined with other interventions (eg, psychotherapy or psychological support) as long as the intervention was given to MDMA and comparator participants equally.
- Comparator was any active or inactive comparator (eg, inert placebo, active placebo, active control).
- Reported one or more of the efficacy and/or safety-related outcomes listed below:
    - Efficacy: Change in PTSD-specific outcome measure (eg, PTSD severity score)
    - Safety: Mortality, hospitalization, psychiatric adverse events, QT interval changes, other serious adverse events, peak changes in vital signs on the day of receiving MDMA
- Study was published with sufficient detail to verify that it meets eligibility criteria (see note about abstracts in the exclusion section below)
    - We considered studies published as a poster only if there was sufficient detail reported. Otherwise, we treated the posters as abstracts.
    - We included studies published in other non-journal formats (eg, from a clinical trial registry site) when there was sufficient detail reported.
- Studies that published, registered, or presented from 2010 to present.

Studies meeting any of the following criteria were excluded:

- Studies published only as an abstract.
    - Owing to the short time for completion of this project, we were not able to reach out to investigators to collect additional information. However, this may be considered in future phases if applicable.
- Studies reporting findings from a subset of non-randomized patients only (eg, of the total randomized PTSD cohort, the study only reports the effects of the subset of participants with comorbid alcohol use disorder). These types of studies were excluded because the hypotheses being tested were observational in nature and not experimental. (A review that includes observational studies may be considered in future phases if applicable).

2.3 Data Extraction

Select participant and trial characteristics, efficacy outcomes, and safety outcomes were extracted into by a single review author into a data collection form. When applicable, multiple sources (eg, published text, information from ClinicalTrials.gov, and the study protocol) were used to collect trial outcomes and methodology. Authors attempted to note when deviations between multiple sources occurred. For feasibility, data collection was performed by a single review author in consultation with one or more other authors as needed.

We prioritized collecting outcome data from the blinded study periods, which contained a control arm, over other open-label non-controlled study periods (eg, open-label follow-up, which also often occurred after cross-over of comparator groups to MDMA-assisted therapy). The blinded trial period was given priority due to it being the trial period of the highest methodological rigor, and the need to be selective due to time constraints of the Task Force. Selected additional information from follow-up periods was reported in the phase I annotated bibliography.

Additionally, we prioritized collection of between-group comparisons (ie, active MDMA versus control comparisons) for outcomes of PTSD-specific instrument scores (ie, tools for measuring PTSD severity) from intention-to-treat (ITT) analyses. If between-group comparisons were not available, other relevant reported information was collected. For example, descriptive statistics for the change from baseline for each study arm. If an ITT analysis was not reported, information from the next most similar analysis was collected (eg, modified ITT). When applicable, we collected both continuous and dichotomous measures for PTSD-specific symptom scales. Point estimates, measures of variation (eg, confidence intervals or standard deviation), and/or P-values for hypothesis tests were collected when reported.

For safety outcomes, we collected and classified serious adverse events (SAEs) as classified in ClinicalTrials.gov or as classified in the published trial. Although we prioritized collection of SAEs from the blinded study periods, we also noted additional SAEs reported during the open-label study periods. Other collected adverse events (AEs) included psychiatric AEs, changes in vital signs on the day of MDMA administration, information about QT interval prolongation, and other emergent non-serious AEs. When applicable, reported safety information was reconciled between multiple reporting sources for the same trial. For unpublished trials, safety results were extracted from available data reported in the ClinicalTrials.gov record for the study. In cases of published and unpublished report sources, information from the published sources (ie, journal article) was prioritized; but, if additional relevant information was reported from the unpublished source or if we were unable to extract information from

the blinded study period of the published record, safety results were collected from the unpublished record. AEs were collected as the number or percentage of affected participants.

A pre-specified list of patient and trial characteristics was collected. This included the number of randomized participants, the number of evaluated participants for various efficacy or safety assessments, and select baseline characteristics (ie, mean age, percentage female, PTSD severity and duration, prior PTSD treatments). Information about study design was collected including pertaining to randomization, blinding, country of study conduct, and phase of the trial. Other collected details include the active MDMA and comparator regimens used during the blinded study period, as well as details about the number and duration of psychotherapy sessions, when available. Information about the psychotherapy setting on the day of study drug administration, training and credentials of therapists, additional details about the psychotherapy modality, and safety/monitoring protocols were extracted from the phase 3 trial or its supporting materials (ie, the MDMA-assisted therapy manual and study protocol for the phase 3 trial).

2.4 Risk of Bias Assessment

Risk of bias (ROB) among primary RCTs was assessed using 2 approaches: the domain-based approach described in the text by Page et al [36] that was adapted from Cochrane ROB tool, [41] and the Jadad scoring system.[42] The approach described by Page et al. includes assessing a level of risk (high, unclear, or low) to 4 bias components with empirical evidence that they exaggerate treatment effects including (1) random allocation sequence generation, (2) allocation concealment, (3) blinding (at the level of participants, clinicians, and outcome assessors), and (4) attrition.[36] We supplemented this with a fifth element, which addressed evidence of selective outcome reporting based on discrepancies between different reports from the same trial. The Jadad score assigns a score based on the likelihood of bias arising from randomization (0-2 points), blinding (0-2 points), and attrition (0-1 points). A score of 0 indicates a high likelihood of bias whereas a score of 5 indicates a low likelihood of bias.[42]

We also supplemented the structured bias assessments with 3 additional assessments: 1) an assessment of adherence to the study drug (or control) and to psychotherapy, 2) assessment of fidelity to the psychotherapeutic model, and 3) an assessment of factors related to potential funding bias.

Information from multiple reporting sources including the published trial, study protocol, and/or ClinicalTrials.gov record. In general, assignment of “high risk” indicates that the trial had a method or factors known to introduce bias (eg, lack of true randomization, probable investigator knowledge of allocation concealment, lack of blinding, and high or differential attrition rates between study arms). “Unclear risk” is typically assigned when there is insufficient information to evaluate the level of risk. Whereas “low risk” indicates the investigators reported a sufficient method or factors that minimize that minimize the ROB. Refer to **Appendix B Table B1** for details on how the ROB was determined.

3.0 RESULTS

3.1 Bibliographic Database Search Results

Our previous phase I report with literature searches in Embase and Medline encompassed 15 records of MDMA for PTSD to bring into screening for the phase II report. The supplemental literature search in CENTRAL, PsycINFO, and MAPS Investigator Brochure (grey literature) identified 110 additional records

for screening. Of these, 45 records were moved to full-text records review, from which 11 records met our inclusion criteria. The 11 included records comprise 8 primary RCTs of MDMA for PTSD, and 3 summary studies of various subsets of these RCTs. The top 3 most common reasons for exclusion after full-text review were the publication being a duplicate of an included study (n=12), registered trials that are not yet complete (n=5), and studies without a comparator (n=7). Refer to **Appendix C Figure C1** for a PRISMA diagram showing the numbers of records identified, screened, included, and excluded including the primary reason for exclusion.

3.2 Overview of the Design of Included Studies

Our search found 8 RCTs and 3 summary studies of various subsets of the same RCTs of MDMA-assisted psychotherapy for treatment of PTSD. Altogether, the 8 RCTs (one phase 3 trial and 7 phase 2 trials) randomized 123 participants to active[‡] MDMA, and 78 participants to control.[32,43-49] These trials were small studies, with the phase 2 trials ranging from 5-28 enrolled participants[43-49] and the largest being the phase 3 trial with 91 total participants.[32] Two of the phase 2 trials randomized participants to 2 active MDMA regimens (ie, medium and high dose), whereas the remainder of the trials, including the phase 3 trial, had 1 active MDMA study arm.[46,47] Each RCT was triple-blinded, including masking of participants, site staff/providers, and primary efficacy outcome assessors.[32,43-49] One exception to the blinding is a small unpublished phase 2 trial (NCT01689740) that incorporated a partial open-label treatment period for 2 MDMA-treated participants for the purpose of standardizing the MDMA-assisted therapy approach prior to enrolling additional participants.[45] Each phase 2 trial also included an optional open-label period following the blinded period in which participants could voluntarily receive additional MDMA-assisted therapy. [43-49] However, our report focuses on results from the blinded period, given that these comparisons provided the only evidence without controls who had received study treatment. The primary efficacy outcome in each was measured approximately 3-8 weeks after the last experimental dosing sessions (when participants received active MDMA or comparator).[32,43-49] Two phase 2 trials were terminated early: one due to poor participant accrual[44] and one due to staff turnover.[43]

After closer review of the 3 summary studies, we determined that the methods described to select studies for inclusion, pool study arms, and conduct statistical analyses raised questions about the validity of those summary hypothesis tests, so we did not rely on them to support our recommendations about MDMA-assisted therapy efficacy and safety. For example, noted concerns included the pooling of study arms without preservation of study-level randomization, and use of unweighted statistical tests for at least some comparisons. Consequently, we use the summary studies to describe the study populations and to augment information on the frequency of adverse events from phase 2 trials.

Refer to **Table 2** for details about the study design and participant characteristics among included primary phase 2 and 3 RCTs. **Appendix D Table D1** elaborates on this table, including more details about the participant eligibility criteria and interventions. **Appendix D Table D2** includes an overview of the participant characteristics and trials included by the 3 summary studies.

[‡] *We use "active MDMA" to refer to MDMA dosages considered to be therapeutic by MAPS investigators. Generally, these are initial MDMA-assisted therapy session dosages ≥ 75 mg. Whereas, initial dosages of MDMA 25-40 mg are referred to as "active placebo" by MAPS investigators, and considered to have no or little therapeutic activity with therapy for the treatment of PTSD.*

Table 2. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT	Study Design[a] Time of primary endpoint measurement after last experimental session	PTSD Population and Select Baseline Characteristics	Treatment Groups[b] (n randomized) *Each drug given in combination with manualized therapy*	Number of Drug-assisted Therapy Sessions Overall # therapy sessions (total hours of therapy)[c]
Mitchell 2021[32,50] NCT03537014	Phase 3 R, TB, PC trial ~8 wks (18 wks from BL) after the 3rd session	Adults with severe chronic PTSD • Mean BL CAPS-5 TS (SD) = 44.1 (6) • Mean PTSD duration (SD) = 14 y (12) • 21% with dissociative PTSD subtype • 88% with multiple-trauma history • 2.2% without pre-study therapy • 32% with lifetime history of MDMA use	MDMA 80-120 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n=46) **Vs** Matched inert placebo (n=45)	3 drug-assisted sessions ~15 total therapy sessions (42 hours)
Unpublished[44] NCT01958593 *Terminated early due poor participant accrual rate*	Phase 2 R, TB, PC trial 4 wks after the 2nd session	Adults with severe chronic PTSD with ≥ 1 treatment failure • Mean BL CAPS-4 TS NR	MDMA 125 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n=4) **Vs** Matched inert placebo (n=2)	2 drug-assisted sessions ~11 total therapy sessions (29.5 hours)
Unpublished[45,51] NCT01689740	Phase 2 R, TB/OL[d], APC trial 8 wks after the 2nd session	Adults with moderate-severe chronic PTSD with ≥ 1 treatment failure • Mean BL CAPS-4 TS NR	MDMA 125 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n=5) **Vs** Low-dose MDMA 25 mg, plus supplemental half-dose 1.5-2.5 h later (n=3)	2 drug-assisted sessions ~11 total therapy sessions (unknown length)
Ot'alora 2018[46,52] NCT01793610	Phase 2 R, TB, APC, dose-finding, trial 4 wks after the 2nd session	Adults with moderate-severe chronic PTSD with ≥ 1 treatment failure • Mean BL CAPS-4 TS (SD) = higher-dose MDMA: 94 (20; med-dose MDMA: 94 (20); low-dose MDMA: 85 (8) • Mean PTSD duration (SD) = 29 y (18) • Majority with multiple-trauma history • 0% without pre-study therapy • Prior MDMA use NR, but enrolled participants were required to not have used MDMA ≥ 5 times/lifetime, or during the 6 months before the trial	MDMA 125 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n=13) **Vs** MDMA 100 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n=9) **Vs** Low-dose MDMA 40 mg initial dose, plus supplemental half-dose 1.5-2.5 h later (n = 6)	2 drug-assisted sessions ~11 total therapy sessions (29.5 hours)
Mithoefer 2018[47,53] NCT01211405	Phase 2 R, TB, APC, dose-finding trial 4 wks after the 2nd session	Adults with moderate-severe chronic PTSD from service occupation-related trauma with ≥ 1 treatment failure • Mean BL CAPS-4 TS (SD) = higher-dose MDMA: 90 (17); med-dose MDMA 82 (17)/low-dose MDMA: 87 (14) • Mean PTSD duration (SD) = 7 y (5) • 85% with military-associated trauma • 4% without pre-study therapy • 23% with prior MDMA exposure	MDMA 125 mg initial dose, plus supplemental half-dose 1.5-2 h later (n=12) **Vs** MDMA 75 mg initial dose, plus supplemental half-dose 1.5-2 h later (n=7) **Vs** Low-dose MDMA 30 mg initial dose, plus supplemental half-dose 1.5-2h later (n=7)	2 drug-assisted sessions ~11 total therapy sessions (29.5 hours)

Abbreviations: APC, active placebo-controlled (eg, low-dose MDMA); BL, baseline; CAPS, clinician-administered PTSD scale; MAPS, multidisciplinary association for psychedelic studies; MDMA, 3,4-methylenedioxymethamphetamine; med, medium dose; NR, not reported; OL, open-label; PC, (inert) placebo-controlled; PTSD, post-traumatic stress disorder; R, randomized; TB, triple-blind; TS, total score; Vs, versus; y, years; wks, weeks

Table 2. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) **NCT**	**Study Design[a]** **Time of primary endpoint measurement after last experimental session**	**PTSD Population and Select Baseline Characteristics**	**Treatment Groups[b]** **(n randomized)** ***Each drug given in combination with manualized therapy***	**Number of Drug-assisted Therapy Sessions** **Overall # therapy sessions (total hours of therapy)[c]**
Oehen 2013[48,54] NCT00353938	Phase 2 R, TB, APC, trial 3 wks after the 3nd session	Adults with moderate-severe PTSD considered treatment-resistant (prior failure of ≥ 6 months of psychotherapy and ≥ 3 months of SSRI therapy) • Mean BL CAPS-4 TS (SD) = active MDMA: 63 (8); low-dose MDMA 66 (14) • Mean PTSD duration (SD) = 7y (5) • Varying index traumas; majority (50%) with childhood sexual abuse • Mean (SD) of 86 (71) months of prior psychotherapy • 8.3% with prior MDMA exposure	MDMA 125 mg initial dose, plus supplemental half-dose 2.5 h later (n=9) **Vs** Low-dose MDMA 25 mg initial dose, plus supplemental half-dose 2.5 h later (n=5)	3 drug-assisted sessions ~15 total therapy sessions (unknown duration)
Mithoefer 2011[49,55] NCT00090064	Phase 2 R, TB, PC trial 8 wks after the 2nd session	Adults with moderate-severe, chronic, PTSD from military- or crime-related trauma after ≥ 1 treatment failure • Mean BL CAPS TS (SD) = 79 (22) • Mean PTSD duration (SD) = 21 y (14) • Varying index traumas; sexual assault or childhood sexual abuse most common • Mean (SD) 59 (22) months with prior psychotherapy • 48% with prior MDMA use	MDMA 125 mg initial dose, plus supplemental half-dose 2-2.5 h later (n=15) **Vs** Matched inert placebo (n=8)	2 drug-assisted sessions ~12 total therapy sessions (31 hours)
Unpublished[43] NCT00402298 *Terminated early due to staff turnover*	Phase 2 R, TB, APC trial 8 wks after the 2nd session	Adults with PTSD from war or terrorism trauma that persists after ≥ 1 treatment failure • Mean BL CAPS-4 TS (SD) = NR • Prior MDMA use NR, but enrolled participants were required to not have used MDMA ≥ 5 times/lifetime, or during the 6 months before the trial	MDMA 125 mg initial dose, plus supplemental half-dose 2-2.5 h later (n=3) **Vs** Low-dose MDMA 25 mg initial dose, plus supplemental half-dose 2-2.5 h later (n=2)	2 drug-assisted sessions ~8-10 total therapy sessions (18-27 hours)

[a] Description reported is for the blinded, controlled trial period. Phase 2 trials also included an open-label period following the blinded period that included additional doses of MDMA, and exposure of the control arm to active-dose MDMA.

[b] Treatment groups are based on the drug administered during each experimental therapy session. **Doses of MDMA or control were given as an initial dose at the start of the experimental therapy session, and if tolerated, an optional second dose (at half the dosage of the original dose) was given approximately 1.5-2.5 h later.**

[c] Therapy was delivered during non-drug assisted sessions (ie, preparatory and integrative sessions), and drug-assisted sessions (ie, experimental sessions assisted by active-dose MDMA or control), and delivered to participants by co-therapists. Therapy was manualized, and followed a non-directive approach. The overall number of therapy sessions is the total of the drug-assisted and non-drug assisted sessions, and the total hours of therapy is an approximation of the total duration of all therapy sessions.

[d] Two participants in the active MDMA arm received open-label treatment, and the remaining participants were blinded.

Abbreviations: APC, active placebo-controlled (eg, low-dose MDMA); BL, baseline; CAPS, clinician-administered PTSD scale; MAPS, multidisciplinary association for psychedelic studies; MDMA, 3,4-methylenedioxymethamphetamine; med, medium dose; NR, not reported; OL, open-label; PC, (inert) placebo-controlled; PTSD, post-traumatic stress disorder; R, randomized; TB, triple-blind; TS, total score; Vs, versus; y, years; wks, weeks

3.2.1 Study Drug Dosages

The control arm for 3 RCTs, including the phase 3 trial, was matched inactive placebo,[32,44,49] and the remaining 5 trials used "active placebo,"[43,45-48] both administered in combination with non-directive manualized therapy in a manner identical to the active MDMA arms. Active placebo was low-dose MDMA (ie, MDMA 25-40 mg per initial dose administration).[43,45-48] The rationale for using the low-dose MDMA comparator is that it may assist with maintaining blinding as participants may still exhibit subjective MDMA-related effects but are unlikely to experience the full catalytic effect.[48,56] Active MDMA was delivered orally in divided doses during 2-3 intermittent psychotherapy sessions separated by 3-5 weeks. For the phase 2 trials, the divided doses typically consisted of an initial dose (75-125 mg MDMA) at the start of a 6-8 hour session and a second "optional" supplemental dose (half of the first dose, ie, 37.5 mg to 62.5 mg MDMA) 1.5 to 2.5 hours after the initial dose.[43-49] The summary study including 6 of the 7 phase 2 RCTs reported that 90.9% supplemental doses were administered.[33] The total active MDMA dose per psychotherapy session across the trials ranged from 112.5-187.5 mg, accounting for the supplemental doses.[32,43-49] The phase 3 trial, which was informed by results of the prior phase 2 trials, was designed to administer MDMA during 3 psychotherapy sessions due to analyses suggesting greater benefit with 3 versus 2 MDMA-facilitated psychotherapy sessions. Similar to, but distinct from the phase 2 trials, active MDMA for the phase 3 trial included a flexible dosage regimen consisting of an initial dose of 80 mg during the first psychotherapy dosing session, and escalation to 120 mg (if tolerated) during the second and third dosing sessions. Furthermore, a supplemental half-dose (relative to the initial dose) was administered in each treatment session 1.5-2.5 hours later (as tolerated). In the active arm of the phase 3 trial, 1 participant chose not to take the supplemental dose but this was not due to tolerability issues; and 2 participants in the active arm chose to not escalate to the 120 mg dose, remaining at the 80 mg dosage.[32]

3.2.2 Study Psychotherapy[§] Characteristics

Psychotherapy in each trial was delivered by 2 trained therapists, usually a male and female pair, according to the manualized MAPS-developed protocol[56]; two possible exceptions are a phase 2 trial (NCT00353938) that possibly did not use trained therapists[33] but still reported delivering the MDMA-assisted therapy per protocol, and a second unpublished phase 2 trial (NCT00402298) lacking a study protocol for verification of details of the psychotherapy deliverers and regimen.[43] According to the summary study of 6 phase 2 RCTs, the same therapist dyad was paired with a given participant during the trial[33]; however, it is likely but uncertain if this was the case for the phase 3 trial. Refer to **Section 3.5.2** for additional details about the training of therapists for the phase 3 trial.

In each trial, the psychotherapy included drug-assisted and non-drug assisted therapy sessions delivered during preparatory, experimental (when MDMA/control was administered with non-directive psychotherapy), and integrative therapy sessions.[32,43-49] Experimental sessions were delivered in a comfortable, aesthetically pleasing setting where participants could sit or lay on a futon and optionally

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[§] Note that we use the terms "psychotherapy" and "therapy" interchangeably in this report. MAPS investigators stressed using a non-directive manualized therapy approach during the RCTs; however, it is unclear to the authors of this report whether the "non-directive" therapy occurred only during MDMA/control-assisted sessions, or if this approach was also extended to all therapy sessions.

wear an eye mask and listen to music.[32,43-49] In most cases, participants stayed overnight following experimental sessions and were monitored by a trained attendant overnight.[43,48,54,57-60] Preparatory therapy sessions preceded the experimental sessions, and the integrative therapy sessions occurred following each experimental session. The first integrative session occurred the morning after each experimental session. The number of preparatory, experimental, and integrative therapy sessions varied across the 8 RCTs, ranging from 2-3 preparatory sessions, 2-3 experimental sessions, and 4-9 integrative sessions; this accounts for a total of 18-42 therapy hours (drug- and non-drug-assisted) per participant.[32,43-49] The phase 3 trial used the intensive therapy approach (ie, most therapy sessions), including 3 MDMA-assisted therapy sessions and 15 total therapy sessions (including preparatory, experimental, and integrative sessions) totaling approximately 42 hours per participant.[32] About one-quarter of participants (24/91, 26%) in the phase 3 trial also completed additional integrative therapy sessions,[32] as was allowed by study protocol.[60] Refer to **Section 3.5** for additional details about the MDMA-assisted therapy model, and safety monitoring used during the phase 3 trial.

3.3 Overview of Participant Characteristics

Most of the RCTs enrolled generally healthy adult (≥ 18 years) participants. Among the phase 2 trials, the majority of enrolled participants were required to have moderate-to-severe PTSD symptoms as evidenced by a baseline CAPS-4 score of ≥ 50 (5 phase 2 trials).[45-49] Exceptions include one phase 2 trial that enrolled participants with severe PTSD symptoms (CAPS-4 score ≥ 60) at baseline,[44] and another phase 2 trial (NCT00402298) lacking details about the required CAPS score threshold.[43] Additionally, 6 of the phase 2 trials required participants to have chronic PTSD symptoms lasting at least 6 months, and failure of at least one prior pharmacologic or psychotherapy treatment.[44-49] The trauma history was variable among participants including civilian or military history; 3 phase 2 trials enrolled participants with specific histories including occupation-related (ie, military, police, or firefighter) trauma,[47] military or crime-related trauma,[49] or war or terrorism-related trauma.[43] Screening for eligibility criteria was performed using psychological assessments, physical, and laboratory examinations by "independent examiners," according to the summary study by Mithoefer et al.[33] A specific list of exclusion criteria was not available for every phase 2 trial, but when specified, participants with high-risk psychiatric conditions (eg, psychotic disorders, personality disorders, active substance use disorders, high suicide risk) and high-risk cardiovascular conditions (eg, uncontrolled hypertension, other significant cardiovascular or cerebrovascular conditions) were excluded.[32,43,46-49] Prior to starting MDMA-assisted therapy, the majority of phase 2 and phase 3 trial participants were required to taper off psychoactive drugs including those for treatment of PTSD.[32,33]

The pooled demographics of participants from 6 of 7 of the phase 2 trials (n=105) showed that overall mean age was 40.5 years with slightly more than half of participants being female (58.5%), and the majority reporting as White (87.6%). The mean duration of PTSD symptoms was about 18 years. Nearly all participants had tried at least 1 psychotherapy modality prior to study (only 2 participants had not), and some participants had tried sertraline (33%) or paroxetine (17%)[**]. Pooled demographics from 4 of the phase 2 trials showed that participants tended to have significant depressive symptoms, as evidenced by a mean baseline Beck Depressive Inventory (BDI)-II total score of 29. The lifetime accounts

[**] *The summary study investigators report that participants could have tried other non-FDA-approved medications for PTSD symptoms, but they did not report those details.*

of suicidality based on the Columbia-Suicide Severity Rating Scale (CSSRS) indicated participants had a significant history of suicidal ideation (87%), serious suicidal ideation (37%), or suicidal behavior (31%).[33]

The phase 3 trial enrolled similarly physically healthy participants as the phase 2 trials, with allowance for some mild, stable chronic conditions (eg, well-controlled hypertension, hypothyroidism, or type 2 diabetes mellitus without evidence of significant cardiovascular disease). Participants were diagnosed as having PTSD meeting *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5) criteria, and had chronic (≥ 6 month), severe (defined as having CAPS-5 total score ≥ 35) symptoms. The phase 3 trial population (n=90) had a mean age of 41 years, and the majority were female (66%), white (77%), and non-Hispanic/Latino (90%). Mean duration of PTSD symptoms was 14 years, and 21% of participants were considered to have the dissociative PTSD subtype (of note, 29.5% of placebo arm compared to 13% of the MDMA arm had this subtype). Participants had a variety of PTSD causes (developmental trauma [84%], combat-related trauma [12%], and/or multiple trauma [88%]). Although prior treatment failure was not required, only 2 participants (2.2%) did not have a history of psychotherapy, and some participants were taking sertraline (19%) or paroxetine (7%) before the study. Most of the participants had comorbid major depression (91%); the total population baseline mean BDI-II score was 33. Most participants had also experienced suicidal ideation during their lifetime (92%), with a lower percentage of participants reporting lifetime serious suicidal ideation (41%), or lifetime suicidal behavior (32%). Study arms were well balanced with respect to comorbid major depression, disability, CAPS-5 score at baseline, and pre-study SSRI (paroxetine or sertraline) use.[32]

3.4 Ongoing Phase 3 Trial of MDMA-assisted Therapy for PTSD

MAPS is conducting a second multisite, blinded, placebo-controlled phase 3 trial (NCT04077437) that aims to enroll approximately 100 adult participants with at least moderate PTSD severity at baseline. Based on information reported on ClinicalTrials.gov, the design of the study appears highly similar to the completed phase 3 trial, including the studied intervention, inert placebo comparator, outcomes measured, and duration of the study.[61] One observed difference between the two phase 3 trials is that the second trial aims to include people with less severe PTSD at baseline (at least moderate severity) [61] than the published phase 3 trial (people with severe PTSD).[32] The estimated completion date for the last participant of this trial is March 5, 2023. [61]

3.5 Details about the Psychotherapy Intervention, Setting, Therapist Training, and Safety Monitoring from the Phase 3 Trial

The following sections provide additional details about the MDMA-assisted psychotherapy model, experimental treatment setting, training of therapists, and safety monitoring according to protocols used for the completed phase 3 trial of MDMA-assisted therapy for PTSD (NCT03537014).

3.5.1 MDMA-assisted Psychotherapy

MDMA-assisted therapy is a combined intervention consisting of non-directive psychotherapy augmented by MDMA during one or more therapy sessions. The drug-assisted (experimental) sessions are supported by non-drug (preparatory and integrative) therapy sessions.[56]

MAPS investigators developed a manual for providing MDMA-assisted therapy. Therapists participating in the MAPS trials were trained on this protocol. Although the protocol was updated over the course of

conducting studies included in this review,[56] the general components of the psychotherapy appear to have been consistent.

In the MAPS manual for MDMA-assisted therapy on page 30, the stated **goal of an MDMA-assisted session** is to "…reduce the symptoms of PTSD and improve the overall functioning, wellbeing, and quality of life of the participant."[56] It is further described that "This goal is accomplished by allowing each participant's experience to unfold spontaneously without a specific agenda about its content or trajectory."[56] Therapists conducting MDMA-assisted therapy should primarily facilitate and support the patient rather than be prescriptive directors[56]; thus, the therapy is referred to as "non-directive." During MDMA-assisted therapy, it is expected that the participant's trauma will be discussed. Therapists should prepare participants for this, and ask for permission from the participant to facilitate discussion of the trauma if it does not naturally emerge from the participant.[56]

Like other medication-assisted therapy models,[62] the therapy sessions are divided into 3 types: (1) preparation, (2) experimental, and (3) integration.[56]

- **Preparatory sessions:**
    - Therapists explain the expected process and address any initial participant concerns; the early formation of a therapeutic alliance between the therapist and participant is crucial. Prior to MDMA administration, participants should be made aware that they will likely experience a heightened state of vulnerability. Therapists should teach participants techniques to alleviate somatic discomfort that may arise when processing distressing thoughts (ie, diaphragmatic breathing or other techniques). The MDMA-assisted therapy manual on page 29 also advises therapists to convey to participants "…the experiences catalyzed by MDMA-assisted therapy will likely continue to unfold and resolve over days or even weeks following the MDMA-assisted therapy sessions. After therapy sessions, particular symptoms may even seem to get worse before improving."[56]
    - For the completed phase 3 trial, three 1.5 hour preparatory sessions were completed: session 1 within 1 week of enrollment; session 2 within 3 weeks of enrollment (and ≥ 2 days after session 1); and session 3 one to four days before the first experimental session (and 3-6 days after the baseline CAPS-5 measurement).[60]
- **Experimental MDMA-assisted therapy sessions:**
    - Before administration of MDMA, which occurs near that start of the session, therapists should address any lingering participant concerns. The participant is encouraged to assume a comfortable position on a futon with an eye mask and headphones playing preselected music (mask and headphones are optional). In experimental sessions, like other sessions, the therapists should practice empathic listening and non-directive communication to help the patient explore their feelings. A general target is about a 50:50 divide of the session centered on the participant's inner focus versus interaction between the participant and therapist. If somatic manifestations or distress emerge, the therapists should encourage appropriate soothing techniques (eg, breathing exercises, reassurance, focused bodywork). When it is nearing the end of the experimental session, the therapists may begin integration by encouraging the participant to self-reflect on the experience. A vetted significant other may be allowed to join at the end of the experimental session (to be present during integration).[56]

- Effects from MDMA are expected to persist over hours to days after the session; participants are encouraged to capture this in writing, through artwork, and by recording any memorable dreams. Rescue medication (ie, for acute anxiety that does not resolve with other nonpharmacologic measures) may be administered if needed at the conclusion. Note that it is common for sleep disturbances the night after MDMA ingestion (sedative hypnotics can be used if appropriate).[56]
- For the completed phase 3 trial, there were 3 experimental sessions lasting at least 8 hours each: the first experimental session was 1-4 days after the final preparatory session; the second session was 21-35 days after the first experimental session (and ≥1 day after the third integration session); and third experimental session was 21-35 days after the second experimental session (and 1-7 days after completion of integration session 6).[60]

- **Integration sessions:**
  - These sessions occur after each experimental session (the first session being the morning after the MDMA-assisted therapy session). The purpose is to help the participant process the experimental session and apply the learnings to their life. Having the first integration session the morning after the experimental session helps to manage any immediate difficult reactions. integrative sessions begin with asking the patient to start an active dialogue about what is on their mind. Therapists should discuss what effects to expect (eg, unfolding effects over weeks) and encourage creative or physical processing (eg, art, exercise) of emergent feelings/thoughts/experiences. [56]
  - Outside of the therapy sessions, the therapists should be available by phone (24 hours per day); the clinical study protocol called for brief daily phone contact during the week following the MDMA dosing session.[56]
  - The completed phase 3 trial included nine 1.5 hour integration sessions, with sessions occurring following each experimental session. The first integration session following an experimental session (ie, overall integration session 1, 4, and 7) occurred the morning after the experimental session. The second integrations sessions (ie, overall integration session 2, 5, and 8) occurred 3-14 days after the prior experimental session (and ≥ 2 days before the next integration session). The final integration sessions in the series (ie, overall integration sessions 3, 6, and 9) occurred ≥ 2 days after the previous integration session (and 1-7 days before the next experimental session for integration sessions 3 and 6).[60]

Table 3 gives an overview of the MDMA-assisted therapy psychotherapeutic approach; key components of the therapeutic approach per the MAPS investigators are listed in **Appendix E.**

Table 3. Overview of MDMA-assisted Therapy[a] for Treatment of PTSD[56]

Therapy Session	Characteristics
General description: Non-directive manualized therapy[b] focused primarily on PTSD symptoms. Characterized by empathic listening to facilitate healing from within the participant. It should allow *processing* of trauma, and may incorporate techniques from other therapeutic models (eg, trauma-focused psychotherapies and methods to manage physiologic states) to support the participants and alleviate somatic discomfort.	
1. Preparation	• Introductions of participant, the therapists, and the expected process • Attempt to establish a therapist-participant alliance

Table 3. Overview of MDMA-assisted Therapy[a] for Treatment of PTSD[56]

Therapy Session	Characteristics
Screening and introductory sessions prior to MDMA/control administration *Duration and number of preparatory sessions in the phase 3 trial: Three 1.5 hour sessions[60]*	• Details of trauma not discussed unless brought up by the participant • Address participant questions/concerns to create a safe space
2. Experimental MDMA/control is administered during these sessions *Duration and number of drug-assisted sessions in the phase 3 trial: Three ≥8 hour sessions[60]*	• Therapists address lingering patient concerns prior to MDMA administration, and prepare participants about what to expect from MDMA (eg, onset of effect, and possible subjective effects) • Participant allowed to acclimate to the room prior to administering drug • Within 15 minutes of taking MDMA, patients are encouraged to lay on a futon with eyeshades and headphones playing preselected music • Therapists focus on providing empathic presence; non-directive invitation may be used to encourage patient exploration • Therapists to check-in with participant 60 minutes after MDMA ingestion (if they have not communicated yet) • Approximately 50:50 split between participant inner focus, and interaction with the therapist • As the acute MDMA effects wear off (ie, toward the end of the session), therapists begin to encourage participants to self-reflect on their experience • Therapists should verify the participant's physical and emotional stability prior to separation at the end of the session
3. Integration These sessions occur between MDMA/control dosing sessions. Their general purpose is to help patient's process their experience during the drug-assisted therapy session and apply it to their life. *Duration and number of integration sessions in the phase 3 trial: Nine 1.5 hour sessions, with 3 occurring after each experimental session[60]*	• Therapists should be responsive to participant needs (eg, only encouraging the participants' integrative transformation, versus redirection of possible problems like shame) • Therapists continue to offer support and encourage the patient to self-reflect during their daily lives (eg, through art, exercise, going in nature) • The first integration session is the morning after the experimental session • Focused bodywork may be used to manage somatic manifestations (eg, tension, psychomotor agitation) • Therapists should inform the participants that after-effects will unfold over coming weeks • Therapists should emphasize their availability for support, and provide a way to contact them • After completion of the entire protocol, the therapists may encourage seeing another therapist as appropriate • Social support should be in place

Abbreviations: MAPS, multidisciplinary association for psychedelic studies; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder;

Table 3. Overview of MDMA-assisted Therapy[a] for Treatment of PTSD[56]

Therapy Session	Characteristics

[a] Based on the MAPS organization's "…Manual for MDMA-assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder" version 8.1 (August 2017). The first version of this protocol was published in May 2005. Refer to the MAPS manual for details about this approach (including the appendix which contrasts MDMA-assisted therapy with evidence-based psychotherapy for treatment of PTSD).

[b] MAPS usually describes the psychotherapy model as being a "non-directive manualized" approach; and the overall therapy includes preparatory, experimental (MDMA-assisted therapy), and integratory sessions. However, it is unclear to the writers of this report whether the "non-directive manualized" psychotherapy is intended to only refer to the MDMA/control-assisted sessions or all sessions; we generally use this term to refer to the style of the overall psychotherapeutic model.

Therapists and participants signed an agreement prior to starting therapy that addresses therapist and participant responsibilities; while some of the required components by MAPS may be due to clinical trial participation, some of the components could be incorporated into non-trial MDMA-assisted therapy agreements. For example, participant agreement to forgo harmful behaviors, therapist agreement to provide a supportive and safe environment, agreements about any use of supportive touch, and that at least 1 therapist will be in the room with the participant at all times.[56]

3.5.2 Therapist Training and Background

Therapist teams, including one male and one female when possible, provided MDMA-assisted therapy for PTSD in MAPS-funded RCTs.[33,60] The MAPS manual recommends that therapists providing MDMA-assisted therapy are trained to provide MDMA-assisted therapy according to their protocol, and also possess prior training and experience as therapists.[56] Therapists participating in the phase 3 MDMA-assisted therapy trial (Mitchell et al 2021) were at least Master's program trained, and at least 1 of the 2 therapists was licensed to provide therapy in the study location.[32] The phase 3 trial required therapists to complete a 5-part 67 hour and 9 day training program divided as follows: "…an online course (15h), a training course (5d), experiential learning (3d), role playing (1d), and supervision (52 h)."[32] Part of the therapist training included adherence criteria for delivery of psychotherapy that varied by therapy visit.[60] On page 12 of the therapy manual, Mithoefer et al mentions that therapists should have prior experience in providing at least some other types of therapy for treatment of PTSD, which may be incorporated into the MDMA-assisted therapy:

> "…Prolonged Exposure (PE), Cognitive Processing (CPT), Eye Movement Desensitization and Reprocessing (EMDR), and psychodynamic psychotherapy" and "…Internal Family Systems (IFS), Voice Dialogue, Psychosynthesis, Hakomi, Sensorimotor Therapy, Holotropic Breathwork, Jungian psychology, Buddhist psychology, and Virtual Reality."[56]

Additional background recommended for therapists is culturally-sensitive communication skills.[56] At least one member of the therapist dyad should be equipped to address somatic symptoms arising during therapy (eg, breathing techniques as part of Holotropic Breathwork), facilitate relaxation (eg, diaphragmatic breathing), and have familiarity with any music that will be used during a therapy session.[56] Therapists should be trained to support transpersonal experiences and multiplicity which may emerge during therapy.[56]

3.5.3 Therapeutic Setting

The therapeutic setting for MAPS-directed MDMA-assisted therapy included the physical place where therapy sessions occurred, and also other considerations such as social support for the participant and non-physical components like music.[56] The protocol for the setting is as follows:

- **Physical components**: The setting was inviting, quiet, comfortable, and aesthetically pleasing (eg, containing flowers). The participant was allowed to acclimate to the setting prior to drug administration. During therapy, the therapists should position themselves near the participant with the participant lying in one of two positions (pages 15-16): "…on a flat futon without sides, with their head against the wall"[56] (therapists may be on either side of the participants head or on the same side) or "…on a sofa or futon with one side against the wall…"[56] (therapists sit on the same side facing the participant). Throughout the session, participants had the option to wear eye shades and/or listen to headphones playing predetermined music.[56]
- **Social support:** Therapists facilitated placement of the participant's social support network before starting therapy. One way members of the social support network helped was by being a supporting listener (eg, after therapy sessions and/or during preparation or integration sessions). Participants were educated to anticipate that some members of their social support network may have negative preconceptions of MDMA-facilitated therapy, and to exercise caution about with whom they share their experiences. Another encouraged support mechanism was having participants write down their experiences in a journal.[56]
- **Music:** Participants had the option to listen to music, have silence, or alternate between the two. Therapists pre-selected the music, which varied in tempo and was adjusted as-needed by the therapist or based on participant request during therapy sessions. While participants could have requested adjustments of music and even bring music they wanted to use during the session, it was recommended that participants not overly fixate on controlling the music.[56]

3.5.4 Safety Monitoring During the Phase 3 Trial

The MAPS-directed manual for MDMA-assisted therapy addresses many psychological and physical safety components for before, during, and after therapy sessions. **Information in the following paragraphs describes some of these components, but this list should not be considered exhaustive.**

The therapist-participant agreement included some specific safety clauses such as (1) an overnight stay after experimental sessions (required by some but not all clinical trial protocols), (2) the presence of at least 1 therapist with the participant at all times, and (3) daily phone contact for up to 1 week after an experimental session. Therapists were trained to assess for participant's physical and emotional stability after sessions, and were available by phone all day and night (24 hours).[56]

The phase 3 clinical trial Included the following phases, which assisted with achieving the intended balance of safety: (1) screening period over 7-28 days (included initial phone screen and verification of eligibility criteria in-person); (2) preparatory period of 1-11 weeks depending on need to taper medications (including baseline assessment, tapering of medications, and preparatory therapy); (3) treatment period for ~12 weeks (including experimental and integrative therapy sessions); (4) follow-up for 4 weeks after the last integration session; and (5) a planned long-term follow-up extension for up to 12 months after the final experimental session.[60]

Sites participating in the phase 3 clinical trial (NCT03537014) were required to have a physician available to assess participant safety during screening; additionally, sites were required to have someone licensed for delivery of controlled substances.[60] The setting had access to immediate Basic Cardiac Life Support (BCLS), and relatively rapid Advanced Cardiac Life Support (ACLS). This included tools to measure blood pressure and heart rate at the ready. Participants were advised to drink electrolyte-containing drinks, but not to exceed 3 liters during one session. Therapists advised participants to rise slowly when going from sitting to standing, and also prevent falls during movement.[56]

Key safety monitoring included checking vital signs, and monitoring for psychological distress including suicidal ideation using the Columbia Suicide Severity Rating Scale (CSSRS). Participants were required to fast overnight prior to receiving MDMA to minimize metabolic activation, and due to the formation of MDMA nitroso-derivatives in the presence of nitrites and nitrates in food.[60]

Enrolled participants in the phase 3 trial were to discontinue the study drug for any of the reasons listed in **Table 4. Table 5** summarizes physical and mental safety monitoring prior to, during, and after MDMA (or placebo) delivery according to the protocol for the phase 3 trial.

Table 4. Planned Safety Reasons for Participant Discontinuation from the Phase 3 trial (NCT03537014)[60]

Specified Safety-related Criteria for Discontinuation after meeting Eligibility criteria
• Pregnancy, or development of other safety-based exclusion criteria (these participants were allowed to complete integrative therapy sessions) • Participant preference to discontinue • Discontinuation by study site (eg, based on clinical judgment of the participant's best interest)

Table 5. Safety Monitoring During the MDMA for PTSD Phase 3 Trial (NCT03537014)[60]

Time Period and Requirements or Monitoring
Prior to MDMA/placebo administration

• Enrolled participants met eligibility criteria[b]
  ○ The screening period verification via medical/psychiatric records and history per participant report; additionally it included urine drug tests, urinalysis, and urine pregnancy screen; laboratory assessments (ie, CMP, CRP, CBC, A:G ratio, BUN: creatinine ratio, TSH [free T3 and T4 as needed], HIV serology, %CDT, HCV as indicated); vital signs, ECG and 1-minute rhythm strip; and physical examination including a brief neurological exam. The C-SSRS lifetime version was used at initial screening to assess suicidality.
• Immediately prior to administration of MDMA (or control):
  ○ 10-h fasting required (only non-alcohol liquids allowed)
  ○ No caffeine within 2-h; no nicotine within 6-h
  ○ People of child-bearing potential using reliable birth control
  ○ Prohibited co-medications during study: SSRIs, SNRIs, MAOIs, trazodone, other antidepressants, diphenhydramine
  ▪ Participant's medications were reviewed and approved for continuation during the trial by physicians

Table 5. Safety Monitoring During the MDMA for PTSD Phase 3 Trial (NCT03537014)[60]

Time Period and Requirements or Monitoring
During MDMA/placebo dosing session

• Laboratory and vital signs monitoring pre-dose:
  ○ Urine drug screen, pregnancy test
  ○ BP, body temperature and HR checked 5 minutes before initial and supplemental dose (1.5-2 h later)
• Other monitoring pre-dose:
  ○ Concomitant medication check
  ○ Suicidality assessment (using Since Last Visit C-SSRS)
  ○ Participant is allowed to acclimate to the room prior to administered the drug
• Monitoring during the session post-dose:
  ○ Therapists monitor participant during the session
  ○ Site physician verifies safety for supplemental MDMA/placebo dose
  ○ Participant must be medically and psychiatrically stable to exit the session
• Vital signs checked before end of session
• Suicidality checked before end of session using the Since Last Visit C-SSRS
• Other: Participants allowed to ingest up to 3L of electrolyte-containing fluids, and food was allowed at end of the session

Immediately following MDMA/placebo dosing session
• Participants ± vetted and approved companion stay in an onsite, comfortable room during night following dosing session • A trained attendant monitors the participant during the night after the dosing session   ○ Therapists or site physician available for 24 hour support • Participant driven home the day following the dosing session
Additional Follow-up

• Telephone follow-up by therapy team: on days 2, 4, 6, 7, 8, 10, 12, 14 after each dosing session
  ○ Brief (5-20 min) to assess for AEs and patient well-being including suicidality (via the Since Last Visit C-SSRS)
• Integrative therapy session (the first occurring the morning after each dosing session, followed by 2 additional sessions over approximately 2-3 weeks; 9 total integration sessions over the course of the trial)
  ○ Assess for health changes including suicidality (via the Since Last Visit C-SSRS)
• Therapists provided contact information to participants for as-needed follow-up for 4±2 weeks after the last integrative session
• At study termination: Since Last Visit C-SSRS, weight, BP, changes in health status
• Extension studies will follow-up with enrolled participants for 12 months post-last dosing session

Abbreviations: A:G, albumin to globulin; BP, blood pressure; BT, body temperature; BUN, blood urea nitrogen; CBC, complete blood count; CDT, carbohydrate deficient transferrin; CMP, comprehensive metabolic panel; CRP, C-reactive protein; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; h, hour; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, heart rate; MAPS, Multidisciplinary Association for Psychedelic studies; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder; T2DM, type 2 diabetes mellitus; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone;

[a] Based on the phase 3 trial (MAPP1) protocol finalized in May 2020 (Amendment 4 version 1)

Table 5. Safety Monitoring During the MDMA for PTSD Phase 3 Trial (NCT03537014)[60]

Time Period and Requirements or Monitoring
[b] Enrolled participants met enrollment criteria which included measures for patient safety including provision of contact information for a support person (eg, if needed due to emergent suicidality); well-controlled hypertension or T2DM; treated, stable hypothyroidism; weight ≥ 48 kg; glaucoma that is verified as okay by an ophthalmologist; lack of severe liver disease (stable, treated mild HCV was allowed); and the lack of medical conditions that could be aggravated by a stimulant medication. Additionally participants with certain psychiatric history were excluded, including (Mitchell et al page 1034): "primary psychotic disorder, bipolar I disorder, dissociative identify disorder, eating disorders with active purging, major depressive disorder with psychotic features, current alcohol and substance use disorders…"[63]. People with T2DM lacking a significant cardiovascular history were required to complete additional cardiovascular screening for enrollment (nuclear exercise test, carotid ultrasound). Participants were not allowed to use prohibited medications during the study; and non-approved prohibited herbal supplements, nonprescription, or prescription medications must be discontinued 1 week prior to each dosing session.

3.6 Efficacy of MDMA-assisted Therapy in RCTs

Evidence from 5 small phase 2 trials and a larger phase 3 trial support the use of MDMA to enhance the effects of psychotherapy for attenuation of PTSD symptoms. Large effect sizes on CAPS PTSD severity scores were demonstrated with MDMA treatment versus the control group in the phase 3 trial (Cohen's *d*=0.9 with 3 treatment sessions)[32] and 5 out of 7 phase 2 trials are suggestive for the efficacy of MDMA-assisted therapy over comparator by at least 1 statistical analysis or PTSD-specific outcome. MAPS investigators note that these effect sizes appear larger, by indirect comparison, than other FDA-approved treatments for PTSD (sertraline and paroxetine with effect sizes 0.56 or less versus placebo).[21,32] Though, importantly, a direct comparative study is needed to confirm the suggested findings.

The phase 3 trial, in 90 participants with severe, chronic PTSD, demonstrated that a course of 3 MDMA-assisted psychotherapy sessions, using a flexible dose regimen[††], was superior to 3 placebo-assisted psychotherapy sessions for improving CAPS-5 total severity score at week 18 post baseline (primary endpoint). An additional 11.9 point reduction in the group mean CAPS-5 score resulted with MDMA treatment versus placebo (Cohen's d = 0.91 for the de jure estimand). In the active arm, 4 patients dropped out between the first and third experimental session, compared to 7 in the placebo arm. Nonetheless, both the primary analysis of people completing at least 1 experimental dosing session (*de jure* estimand), and the sensitivity analysis with the *de facto* estimand (effect of treatment as assigned, regardless of adherence) consistently showed the significant difference in MDMA effect versus placebo. The MDMA effect on CAPS-5 was unaffected by factors such as PTSD disease duration, age of PTSD

[††] The flexible dose regimen was as follows: 80 mg MDMA for the initial dose of the first session, and escalation to 120 mg (if tolerated) for the initial dose of the second and third session. Furthermore, a supplemental half-dose (relative to the initial dose) was administered in each treatment session 1.5-2.5 hours after the initial dose (as tolerated). In the active arm, 1 patient chose not to take the supplemental dose but this was not due to tolerability issues; and 2 patients in the active arm chose to not escalate to the 120 mg dose, remaining at the 80 mg dosage.

onset, history of alcohol or substance use disorders, history of severe childhood trauma, or previous SSRI treatment (66% of enrolled participants had a history of SSRI use).[32]

Regarding other clinically meaningful responses, after 3 treatment sessions, a higher proportion of MDMA-treated versus placebo-treated patients no longer met DSM-5 diagnostic criteria for PTSD (67% vs. 32%, respectively) and/or attained remission[‡‡] (33% vs. 5%, respectively). Significant improvements in the secondary endpoint for clinician-rated functional impairment related to work and/or school, social and family settings (measured by SDS) and the exploratory outcome related to depressive symptoms (measured by BDI-II) were also demonstrated for MDMA-assisted therapy relative to placebo.[32] Long-term follow-up data (planned out to 12 months)[60] describing the effect durability is not yet completed or published from this phase 3 trial.

Results of the phase 3 trial are supplemented by 7 small phase 2 trials that examined 2-3 MDMA-assisted therapy (initial active MDMA doses ranging from 75 mg to 125 mg) sessions to inactive or active placebo-assisted therapy (ie, initial doses of 0 to 40 mg MDMA) among adults with moderate-severe, chronic PTSD.[43-49] Five of the 7 phase 2 trials tended to favor or demonstrated statistical superiority of MDMA-assisted therapy versus control with respect to at least 1 PTSD-specific outcome.[45-49] Two phase 2 trials that failed to show a significant difference between MDMA and control were terminated early, enrolling a very small sample (n=5 or 6 each),[43,44] and therefore offer less reliable efficacy estimates.

In the summary study of 6 phase 2 trials (Mithoefer et al), participant data from MDMA 75-125 mg (initial) dosage arms were combined into a single active-dose arm for analysis, while data from the control 0-40 mg (initial) MDMA dosage arms were combined into a single comparator arm for analysis. The combined data showed greater improvement in CAPS-4 score with 2 MDMA-assisted session versus 2 control-assisted sessions. Authors reported that the apparent benefits were not a function of study, patient age, PTSD disease duration, sex, race, or self-reported prior ecstasy use. Following 2 experimental sessions, a higher proportion of MDMA-treated patients no longer met PTSD diagnostic criteria than in the control arm (54.2% vs. 22.6%, respectively). Depression symptom improvement (measured per BDI-II) tended to favor MDMA treatment but the difference was not significant.[33]

Refer to **Table 6** for a summary of primary efficacy outcomes in the phase 3 and phase 2 trials. **Appendix F Table F1** summarizes results from 3 included summary studies that included 3-6 of the 7 included phase 2 RCTs.

[‡‡] Remission was defined as loss of diagnosis and a total CAPS-5 score ≤11

Table 6. Efficacy of MDMA-assisted Therapy for PTSD in Randomized Controlled Trials, 2010-present

Study First Author and Publication Year NCT (MAPS trial name) *Comparison (n randomized)*[a,b]	CAPS Outcome[c]		Dichotomous Response Outcomes		Notes
	CAPS Measure and Timepoint[d]	**Mean Change in CAPS from BL per Arm (SD)** (Between Group Difference and P-value vs Control Group, if provided)	**Response Measures**	**Proportion of Patients with Response (%)**	
Mitchell 2021 [32,50] NCT03537014 (MAPP1) *MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n = 45)*	Change in CAPS-5 total severity score* at 18 weeks after baseline (approx. 8 weeks post **3rd experimental session**/dose)	**Per protocol set:** MDMA, n=42: **–24.4** (11.6) PBO, n=37: **–13.9** (11.5) **BGD in CAPS change for the de jure set** (ie, patients with at least one experimental session; MDMA, n=46; PBO, n=43): **11.9**, (95% CI 6.3, 17.4); **P<0.0001** by MMRM **Sensitivity analysis with the de facto estimand** (ie, effects with drug taken as assigned, regardless of adherence; total n=90) showed the significant difference between arms was maintained; **P < 0.0001** by MMRM	Loss of PTSD diagnosis	**Per protocol set** MDMA: 28/42 (**67%**) PBO: 12/37 (**32%**)	MDMA > PBO for primary endpoint with *d*=0.91 (95% CI 0.44-1.37, de jure set). Significant decreases in change in disability (by SDS) with MDMA vs PBO from baseline to 18 weeks.
			Remission (loss of PTSD diagnosis and CAPS-5 score ≤11)	**Per protocol set** MDMA: 14/42 (**33%**) PBO: 2/37 (**5%**)	
Unpublished[44] NCT01958593 (MP-4) *Terminated Early* *MDMA 125 mg (n=4) for 2 sessions vs PBO (n=2)*	Change in CAPS-4 total severity score* at 1 month post **2nd experimental session** (3-5 weeks post treatment dose)	MDMA, n=4: **–17.3** (13.05) PBO, n=2: **–21.5** (12.02)	NR		
Unpublished[45] NCT01689740 (MP-9) *MDMA 125 mg (n=5) for 2 sessions vs APBO 25 mg (n=3)*	Change in CAPS-4 total severity score* at 1 month post **2nd experimental session** (2 months post treatment dose)	MDMA, n=5: **–34.6** (16.29) APBO, n=3: **–9.0** (15.62)	NR		
Ot'alora 2018[46,52] NCT01793610 (MP-12) *MDMA 125 mg (n= 13) or 100 mg (n= 9) for 2 sessions vs APBO 40 mg (n=6)*	Change in CAPS-4 total severity score* at 1 month post **2nd experimental session**/dose	MDMA 125 mg, n=12: **–26.3** (29.5) MDMA 100 mg, n=9: **–24.4** (24.2) APBO, n=6: **–11.5** (21.2) No overall difference; **P=0.52** by ANOVA **Per protocol set:** MDMA 125 mg, n=9: **–37.0** (20.9); **P=0.01** (compared to APBO by t-test) MDMA 100 mg, n=9: **–24.4** (24.2); **P=0.10** (compared to APBO by t-test) APBO, n=5: **–4.0** (11.9) Significant overall difference (per protocol set); **P=0.03** by ANOVA	Loss of PTSD diagnosis	MDMA 125 mg: 5/12 (**41.7%**) MDMA 100 mg: 4/9 (**44.4%**) APBO: 2/6 (**33.3%**)	Cohen's *d* effect sizes compared to APBO (ITT set): MDMA 125 mg, 0.42 (95% CI –0.57, 1.42) and MDMA 100 mg, 0.37 (95% CI –0.57, 1.42)
			≥30% decrease in CAPS-4 score	MDMA 125 mg: 6/12 (**50.0%**) MDMA 100 mg: 5/9 (**55.6%**) APBO: 1/6 (**16.7%**)	

Abbreviations: ANOVA, analysis of variance; APBO, active placebo as low-dose MDMA; BGD, between group difference; BL, baseline; CAPS-5, Clinician-administered PTSD for DSM-5; CAPS-4, Clinician-administered PTSD for DSM-4; *d*, between-group treatment effect size using Cohen's d; DSM, Diagnostic and Statistical Manual of Mental Disorders; ITT, intention to treat; MDMA, 3,4-methylenedioxymethamphetamine; MMRM, mixed model repeated measures; n, number; NR, not reported; PBO, inert placebo; PDS, posttraumatic diagnostic scale; PTSD, post-traumatic stress disorder; SD, standard deviation; SDS, Sheehan Disability Scale

Table 6. Efficacy of MDMA-assisted Therapy for PTSD in Randomized Controlled Trials, 2010-present

Study First Author and Publication Year NCT (MAPS trial name) *Comparison (n randomized)*[a,b]	CAPS Outcome[c]		Dichotomous Response Outcomes		Notes
	CAPS Measure and Timepoint[d]	**Mean Change in CAPS from BL per Arm (SD)** (Between Group Difference and P-value vs Control Group, if provided)	**Response Measures**	**Proportion of Patients with Response (%)**	
Mithoefer 2018[47,53] NCT01211405 (MP-8) *MDMA 125 mg (n=12) or 75 mg (n=7) for 2 sessions, vs APBO 30 mg (n=7)*	Change in CAPS-4 total severity score* at 1 month post **2nd experimental session**/dose	MDMA 125 mg, n=12: **–44.3** (28.7); **P=0.004** (compared to APBO by t-test) MDMA 75 mg, n=7: **–58.3** (9.8); **P=0.0005** (compared to APBO by t-test) APBO, n=7: **–11.4** (12.7) Significant overall difference ; **P = 0.001** by ANOVA	Loss of PTSD diagnosis	MDMA 125 mg: 7/12 (**58%**) MDMA 75 mg: 6/7 (**86%**) APBO: 2/7 (**29%**)	No statistically significant difference in CAPS change between MDMA 125 and MDMA 75 mg active arms. Cohen's *d* effect sizes compared to APBO (ITT set): MDMA 125 mg, 1.1 (95% CI 0.04, 2.08) and MDMA 75 mg, 2.8 (95%CI 1.19, 4.39)
			≥30% decrease in CAPS-4 score	MDMA 125 mg: 8/12 (**67%**) MDMA 75 mg: 7/7 (**100%**) APBO: 2/7 (**29%**)	
Oehen 2013[48,54] NCT00353938 (MP-2) *MDMA 125 mg (n=9) for 3 treatment sessions vs APBO 25 mg (n=5)*	Change in CAPS-4 total severity score at 3 weeks post **3rd experimental session**	MDMA, n=8: **–15.6** (18.1) APBO, n=4: **–3.2**[e] (15.3) No significant overall treatment effect on CAPS with time; **P=0.066** by ANOVA	NR		**Self-reported PTSD symptoms (by PDS) decreased in the active MDMA arm**, but not in the APBO arm; P = 0.014 for interaction between treatment group and time.
Mithoefer 2011[49,55] NCT00090064 (MP-1) *MDMA 125 mg (n=15) for 2 sessions vs PBO (n=8)*	Change in CAPS-4 total severity score* at 2 months post **2nd experimental session**/dose	MDMA, n=12: **–55.2** (33.54) PBO, n=8: **–20.5** (20.47) Significant overall difference between groups over time by ANOVA with repeated measures **P=0.015.** The difference between groups was demonstrated at 2 months post-dose by multiplicity-adjusted Bonferroni test; **P=0.013.** (assumed to be per protocol set)	Loss of PTSD diagnosis	MDMA: 10/12 (**83.3%**) PBO: 2/8 (**25%**)	Between-group effect size of 1.24 reported (possibly using Cohen's *d* per the methods)
			≥30% decrease in CAPS-4 score	MDMA: 10/12 (**83.3%**) PBO: 2/8 (**25%**)	
Unpublished[43] NCT00402298 *Terminated Early* *MDMA 125 mg (n= 3) for 2 treatment sessions vs APBO 25 mg (n= 2)*	Change in CAPS-4 total severity score at 2 months post **2nd experimental session**	MDMA, n=2: **–0.5** (4.95) APBO, n=2: **–7** (18.38)	NR		**Reported as having data quality issues, so quality of the result is not guaranteed.** This study is not included among any of the summary studies.

***Primary efficacy endpoint**

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] Unless specified otherwise, reported information is from intention-to-treat or modified intention-to-treat population estimates

[c] The CAPS-5 scale scores range from 0-80[32]; moderate-severity PTSD corresponds to a total score of 23-34, and severe PTSD is a total score ≥ 35.[64] CAPS-4 scale scores range from 0 to 136,[65] with moderate severity being a total score of 40-59,[64] and severe PTSD being scores ≥ 60.[66]

[d] The assessment timepoint for response measures is the same as the CAPS timepoint

[d] Change from baseline in CAPS score for APBO reported with a negative value in published report and ClinicalTrials.gov (implying a decrease from baseline), but Figure 2 of the publication suggests this is an error and the difference should be a positive value (baseline APBO mean score was 63.4, and increased to 66.5 at the T2 endpoint according to Figure 2).

Abbreviations: ANOVA, analysis of variance; APBO, active placebo as low-dose MDMA; BGD, between group difference; BL, baseline; CAPS-5, Clinician-administered PTSD for DSM-5; CAPS-4, Clinician-administered PTSD for DSM-4; *d*, between-group treatment effect size using Cohen's d; DSM, Diagnostic and Statistical Manual of Mental Disorders; ITT, intention to treat; MDMA, 3,4-methylenedioxymethamphetamine; MMRM, mixed model repeated measures; n, number; NR, not reported; PBO, inert placebo; PDS, posttraumatic diagnostic scale; PTSD, post-traumatic stress disorder; SD, standard deviation; SDS, Sheehan Disability Scale

3.6.1 Effect Durability at Long-term Follow-up of Phase 2 Trials

Jerome et al conducted a descriptive analysis of 6 out of 7 of the included phase 2 RCTs (NCT00090064, NCT00353938, NCT01211405, NCT01689740, NCT01793610) that included longer-term outcomes among adult participants with moderate-severe chronic PTSD that failed at least 1 prior PTSD treatment. There is a lack of control group since the control arm participants crossed over to receive active MDMA treatment (ie, initial dose of 100-125 mg during MDMA-assisted sessions) after breaking the blinded period. Ultimately, participants included in the analysis (n=105 were randomized, and n=91 [86.7%] completed long-term follow-up) received 1-6 active MDMA sessions, with some having initially received placebo or low-dose MDMA (0-40 mg initial MDMA dose). A majority of participants received 3 active MDMA-assisted sessions (n=71). For 5 trials, long-term follow-up (LTFU) occurred 12 months after the last MDMA-assisted session; long-term follow-up for the sixth trial was at an average of 3.8 years after study completion.[67]

Change in CAPS-4 total severity scores from treatment exit to LTFU suggests stable or improved PTSD symptom severity in the cohort completing LTFU. Upon completion of the open-label trial period, 56% participants no longer met criteria for diagnosis of PTSD (per CAPS-4 criteria). This proportion was also stable or improved after LTFU, with 67% of the participants in the LTFU cohort no longer meeting PTSD diagnostic criteria. At LTFU, 11 participants (12%) in the LTFU cohort had a relapse of PTSD symptoms (relapse was defined as having an initial decrease in CAPS-4 total score by at least 15 points by trial completion and a CAPS-4 score increase by 15 or more points at LTFU). LTFU participant-reported questionnaire responses indicated that the majority of the cohort felt they benefited from MDMA-assisted therapy (97.6%).[67]

Although the response at LFTU of 1 to 3.8 years is encouraging, it is important to keep in mind the limitations of this analysis including the lack of control group, and the possibility of confounding factors (eg, other PTSD treatments during follow-up) that could also explain the response. At LTFU, a high proportion of the cohort reported being in therapy (49%) or taking medications (46% overall; only 5% reporting taking a medication for PTSD). Additionally, the LTFU cohort did not include the entire randomized trial population, and responses were sometimes limited to a subset of the LTFU cohort (eg, responses about other treatments were from n=64 [70% of the LTFU cohort]).[67]

3.7 Safety Events during RCTs

The MAPS investigators summarized safety information from phase 2 and phase 3 clinical trials of MDMA for PTSD in the Investigator's Brochure (14th edition; effective April 1, 2022). According to MAPS investigators, MDMA-associated adverse events (AEs) were most prominent on the day of receiving MDMA, and in most cases, the events did not persist after about 3-4 days. AEs that persisted for longer than 7 days among at least 10% of active MDMA-treated participants in phase 2 trials, and may or may not be MDMA-related, include insomnia, anxiety, fatigue, poor mood, difficulty concentrating, and irritability.[31]

Refer to the following subsections for details about serious adverse events, psychiatric adverse events, other non-serious adverse events, and vital sign changes reported by included trials.

3.7.1 Serious AEs (SAEs)

- No deaths occurred in either treatment group (active MDMA or control) among included RCTs according to ClinicalTrials.gov.[43-45,50,52,53,55] One death (from a recurrence of breast cancer that had been in remission for >10 years) 6 months after active MDMA treatment was reported in the published report of a phase 2 trial (Oehen et al).[48] Refer to **Appendix G Table G1** for SAEs reported during the 8 included RCTs.

  Reported SAEs *during the blinded study period*, per data at ClinicalTrials.gov, included:

  - Suicidality (2 participants in the placebo arm of the phase 3 trial[32,50]; 1 active MDMA participant among phase 2 trials[48])
  - Breast cancer (1 active MDMA participant in a phase 2 trial[52])[§§]
  - Lower limb fracture (1 active MDMA participant in a phase 2 trial[52]) [‡‡]
  - Ruptured ovarian cyst (1 active MDMA participant in a phase 2 trial[52]) [‡‡]
  - Central nervous system metastasis (1 active MDMA participant in a phase 2 trial[48])
  - Clavicle fracture (1 active MDMA participant in a phase 2 trial[55])
  - Syncope (1 active MDMA participant in a phase 2 trial[55])
- Three phase 2 trials that included a total of 21 participants did not report any SAEs during the blinded study period.[43-45] All of the trials (ie, 4 phase 2 trials) reporting SAEs in the active MDMA arm considered the events to be unrelated to MDMA.[46-49]
- One phase 2 trial reported 4 serious AEs during an unknown follow-up period (may include the blinded and open-label follow-up period).[52] These 4 events included extrasystole exacerbation, events of suicidal ideation and depression in the same low-dose MDMA participant,[47] and appendicitis in a low-dose MDMA participant.[53]
  - The SAE of a worsening ventricular extrasystole, considered possibly MDMA-related, was reported during a third MDMA 125 mg session during the open-label trial period.[33] This participant did not receive any additional MDMA doses, and recovered to baseline function after observation in the hospital.[47]
- According to the summary study of 6 phase 2 trials, 1 additional SAE was reported outside the blinded period: 1 event of suicidal behavior before the participant was exposed to MDMA.[33]

3.7.2 Psychiatric AEs

Psychiatric AEs attributed to MDMA during the phase 3 trial include bruxism, restlessness, intrusive thoughts, nervousness, and stress. Insomnia also occurred at a higher rate with MDMA compared to placebo.[32] Four self-reported treatment emergent AEs (TEAEs) that occurred at a higher rate with active MDMA versus control during the blinded study period in the summary study of 6 phase 2 trials were anxiety, depressed mood, irritability, and panic attack.[33]

[§§] There is a discrepancy between ClinicalTrials.gov and the published text for these events. According to the text, these occurred during the open-label dosing period (stage 1 breast cancer), or 12 month observational follow-up period (ruptured ovarian cyst, and fractured lower limb).

The information on suicidality is insufficient to determine whether active MDMA increases the risk of suicidality. In the phase 3 trial, the proportion of active MDMA participants with suicidality (ie, suicidal ideation or behaviors) was similar to, or possibly numerically less frequent than the proportion of placebo participants, depending on the compared event and time period. [32,50] In contrast, a trend toward a higher proportion of participants expressing positive suicidal ideation with active MDMA versus control was found in the summary study of 6 phase 2 RCTs.[33] But study investigators emphasized that a higher incidence of suicidal ideation was found among active MDMA participants at baseline[33]; so, there is uncertainty about whether there is a causal relationship with active MDMA.

Appendix H Table H1 includes a table summarizing psychiatric adverse events occurring during the blinded trial period for each trial. The sections below highlight psychiatric AEs during blinded treatment from the phase 3 trial and summary study of 6 phase 2 trials.

Phase 3 trial

- Psychiatric TEAEs in the phase 3 trial occurring between baseline or first experimental session to study termination (ie, blinded trial period) that were reported more often in the active MDMA group than the placebo group, with approximately a ≥5% difference between treatment groups, were bruxism, restlessness, intrusive thoughts, nervousness, stress, and insomnia. Authors of the considered all of these events except for insomnia as related to MDMA; they did not report anything about the increased insomnia in the published report. In comparison, rates of anxiety, irritability, nightmares, suicidal ideation, and intentional self-injury were reported more frequently (≥5% difference between treatment groups) in the placebo group versus the MDMA group.[32]
- Regarding **suicidality,** although one incident of intentional self-harm related to suicidal ideation was reported in the active MDMA arm, there was no noticeable increase in suicidality in the MDMA arm compared to the inactive placebo arm (6.5% versus 11.4%, respectively) between the first MDMA/placebo dose to study termination.[32] The incidence of suicidal ideation reported in the published article (4.3% for active MDMA vs 6.8% for placebo)[32] is lower than that reported on ClinicalTrials.gov (48% for active MDMA vs 53% for placebo). [50] The reason for this discrepancy is unclear, but it could be either due to differences in the reporting time period or differences in the definition used. Nevertheless, both accounts do not suggest increased suicidal ideation with MDMA.

Refer to **Table 7** for a summary of psychiatric adverse events from the phase 3 trial. The first section reports AEs reported by the published article (Mitchell et al 2021), [32] and the second portion adds additional possible psychiatric AEs for the same trial as reported on ClinicalTrials.gov. Bolded values signify a ≥5% difference between the affected proportions in each treatment group.

Summary Study Results for 6 out of 7 Phase 2 RCTs

- Psychiatric TEAEs that were self-reported by ≥3 participants in either group that occurred after the first dose administration to the day before the third experimental session were anxiety, depression, irritability, and panic attack. Each of these events occurred at a numerically higher rate in the pooled active MDMA (ie, initial dose of 75-125 mg) than the control arm (initial dose of 0-40 mg MDMA) among the phase 2 trials.[33]
- In general, investigators describe that most AEs were mild to moderate severity, and often transient. An analysis of the frequency of AEs daily from the day of dosing to 7 days later supports this conclusions. Although these observations are only descriptive, persistent AEs on day 7 after active MDMA dosing at numerically more frequently than control include, but are not limited to, anxiety,

difficulty concentrating, jaw clenching, increased irritability, low mood and restlessness.[33] Refer to **Appendix H Table H2** for the 7 day analysis summary.

Table 7. Psychiatric Adverse Events of MDMA-assisted Therapy for PTSD from the Phase 3 Trial Mitchell 2021 (NCT03537014)[32,50]

Psychiatric AEs	Active MDMA Number of affected patients (%)	Inert Placebo Number of affected patients (%)
Randomized: MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n = 45) *Safety Analysis:* MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n =44)		
TEAEs[b] reported from the first MDMA/placebo dosing session to study termination[32]		
Bruxism*	**6 (13.0%)**	**1 (2.3%); or 2 (4.6%)** per ClinicalTrials.gov [50]
Restlessness*	**7 (15.2%)**	**0 (0%)**
Intrusive thoughts*	**4 (8.7%)**	**0 (0%)**
Nervousness*	**3 (6.5%)**	**0 (0%)**
Stress*	**4 (8.7%)**	**0 (0%)**
Suicidality (total)	**3 (6.5%)**	**5 (11.4%)**
Intentional self-harm with suicidal ideation	1 (2.2%)	0 (0%)
Suicidal behavior and self-harm	0 (0%)	1 (2.3%)
Suicidal behavior, self-harm and suicidal ideation	0 (0%)	1 (2.3%)
Suicidal ideation	2 (4.3%)	3 (6.8%)
Other possible psychiatric AEs from baseline to study termination with incidence ≥ 5% reported on ClinicalTrials.gov[50]		
Agitation	4 (8.7%)	3 (6.8%)
Anger	6 (13.0%)	6 (13.6%)
Anxiety	**22 (47.8%)**	**25 (56.8%)**
Depressed mood	6 (13.0%)	6 (13.6%)
Depression	4 (8.7%)	4 (9.1%)
Dissociation	2 (4.4%)	3 (6.8%)
Emotional disorder	4 (8.7%)	4 (9.1%)
Emotional distress	2 (4.4%)	3 (6.8%)
Flashback	3 (6.5%)	3 (6.8%)
Insomnia	**29 (63.0%)**	**20 (45.5%)**
Intentional self-injury	**1 (2.2%)**	**5 (11.4%)**
Irritability	**7 (15.2%)**	**10 (22.7%)**
Nightmare	**8 (17.4%)**	**12 (27.3%)**
Panic attack	2 (4.4%)	3 (6.8%)

Table 7. Psychiatric Adverse Events of MDMA-assisted Therapy for PTSD from the Phase 3 Trial Mitchell 2021 (NCT03537014)[32,50]

Psychiatric AEs	Active MDMA Number of affected patients (%)	Inert Placebo Number of affected patients (%)
Suicidal ideation[c]	**22 (47.8%)**	**23 (52.3%)**

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PBO, inert placebo; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the active MDMA group and the control group.

*****Indicates study authors considered the events as related to MDMA based on ≥2-fold incidence higher than placebo

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported here are based on the initial MDMA dose given during experimental therapy sessions. Most participants also received an additional dose at half the initial amount.

[b] Classified as possibly psychiatric by the authors of this report.

[c] It is unclear why these percentages are higher than those reported in the publication. It may be that different severity thresholds were used to classify them or a difference in the duration of the reporting period. Suicidality events reported by the article had to be considered severe, or be associated with self-harm or suicide attempts.

- For psychiatric AEs occurring on the day of the blinded experimental sessions 1 and 2, anxiety, difficulty concentrating, jaw clenching/tightness, low mood, restlessness, and ruminations occurred among a numerically higher percentage of participants in the active MDMA arm versus the control arm. In contrast, increased irritability and insomnia were reported in a higher percentage of the control recipients than the active MDMA recipients.[33]
- Regarding **suicidality,** at baseline (during preparatory therapy before receiving any drug dose), a higher proportion of active MDMA participants expressed suicidal ideation (46%) or suicidal behavior (2%) compared to control participants (16.7% suicidal ideation and 0% suicidal behavior). The proportion of active MDMA participants expressing suicidal ideation was numerically higher than the control group at all reported time periods including dosing, integration visits, and during the first week after the first integration session. The proportion of active MDMA participants with positive ideation after session 2 was 35% versus 7.1% in the comparator arm; 2 active MDMA participants (4.7%) expressed serious ideation compared to 0% for the comparator. On page 2739, the investigators summarize these observations as the following: **"During the treatment phase, suicidal ideation transiently increased in some participants and was more common in the MDMA group, although the causal relationship to the psychotherapeutic processing of traumatic memories or to MDMA itself, or to random group differences could not be determined."**[33]

Refer to **Table 8** for a summary of psychiatric adverse events from the summary study (Mithoefer 2019). Bolded values signify a ≥5% difference between the affected proportion in each treatment group.

Table 8. Psychiatric Adverse Events from a Summary Study[a] (Mithoefer 2019[33]) of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD (NCT00090064; NCT00353938; NCT01958593; NCT01211405; NCT01689740; NCT01793610)

Psychiatric AEs[b]	Active MDMA (Initial Dose of 75-125 mg) Number of affected participants (%)	Control (Initial MDMA Dose of 0-40 mg) Number of affected participants (%)
Randomized and Safety Analysis: MDMA 75-125 mg (n=72) for 2 sessions vs Comparator (MDMA 0-40 mg) (n=31)		
TEAEs[c] reported after the first dose administration to the day before the third experimental session (self-reported; for AEs affecting at least 3 participants)		
Anxiety	**17 (23.6%)**	**3 (9.7%)**
Depressed mood	**6 (8.3%)**	**1 (3.2%)**
Irritability	**3 (5.6%)**	**0 (0%)**
Panic attack	**3 (5.6%)**	**0 (0%)**
Expected reactions reported during blinded experimental sessions 1 and 2[d]		
Anxiety	**52 (72.2%)**	**15 (48.4%)**
Difficulty concentrating	**16 (22.2%)**	**3 (9.7%)**
Increased irritability	7 (9.7%)	4 (12.9%)
Insomnia	**21 (29.2%)**	**12 (38.7%)**
Jaw clenching, tight jaw	**46 (63.9%)**	**6 (19.4%)**
Low mood	**17 (23.6%)**	**4 (12.9%)**
Restlessness	**26 (36.1%)**	**7 (22.6%)**
Ruminations	11 (15.3%)	4 (12.9%)

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] Only includes psychiatric AEs that were collected only during the blinded treatment (ie, not including any open-label follow-up period, if applicable).

[c] Investigators defined TEAEs as events not expected based on prior events in healthy participants OR events that persisted for ≥ 7 days after an MDMA/placebo dosing session.

[d] Participants reporting expected, spontaneously reported AEs during the 6-8 hour experimental session in which active MDMA or the comparator was administered.

3.7.3 Non-psychiatric AEs

Observed non-psychiatric AEs generally align with expected events based on the proposed pharmacology of MDMA. AEs that occurred during the blinded phase 3 trial that investigators attributed

to MDMA were blurred vision, chills, decreased appetite, dry mouth, feeling cold, feeling jittery, frequent urination, hyperhidrosis, increased blood pressure, muscle tightness, muscle twitching, musculoskeletal pain, mydriasis, nausea, non-cardiac chest pain, nystagmus, postural dizziness, pyrexia, somnolence, substance use, and urinary urgency.[32] According to ClinicalTrials.gov, some additional frequent AEs that occurred numerically more frequently with active MDMA than placebo included back pain, dizziness, headache, upper abdominal pain, viral upper respiratory infection, and weakness. [50] Investigators did not find an association between active MDMA and pre-specified adverse events of interest, including abuse liability for MDMA and arrythmia-related cardiac events.[32]

Non-psychiatric AEs reported by the summary study safety analysis of 6 phase 2 trials generally support the types of AEs observed in the phase 3 trial. One possible difference between the phase 3 trial and pooled phase 2 analysis was the incidence of infections; a numerically higher incidence of viral respiratory infections was reported for active MDMA versus inert placebo in the phase 3 trial, [50] but the overall incidence of infections (notably a different outcome) was similar between arms in the phase 2 trials.[33] The significance of this is unclear. An analysis of the incidence of adverse on the day of dosing and for each day after up to 7 days after receiving MDMA or control in phase 2 trials supports that in general, most adverse events are transient, tending to decline in frequency by day 7.[33]

Appendix I Table I1 and Table I2 summarize non-psychiatric AEs that occurred during the blinded trial period for each study. Information below highlights non-psychiatric AEs during blinded treatment from the phase 3 trial and summary study of 6 phase 2 trials, representing the majority of included RCTs.

Phase 3 trial

- The most frequent (≥15%) non-psychiatric TEAEs reported more often in the MDMA arm from the first experimental session to study termination included mydriasis, muscle tightness, nausea, decreased appetite, feeling cold, and hyperhidrosis (excessive perspiration).[32] According to ClinicalTrials.gov, additional frequent (≥15%) TEAEs reported more often in the MDMA arm than in the inactive placebo arm from baseline to study termination included back pain, dizziness, headache, upper abdominal pain, viral upper respiratory tract infection, and weakness (asthenia). [50]
- The investigators report carefully assessing for emergent cardiovascular events indicative of arrythmias or QT interval prolongation. Notably, one participant in the placebo group had an incident of irregular heartbeats and palpitations, whereas none of these AEs occurred among the active MDMA participants of the phase 3 trial. An increased incidence (≥5% higher than placebo) of blurred vision, increased blood pressure, and postural dizziness occurred in the active MDMA group, and investigators considered these events to be related to MDMA.[32]
- Assessing for MDMA abuse potential was also a pre-specified event of interest by investigators. They looked for any events classified as related to abuse, dependence, overdose, addiction, or overdose for MDMA abuse potential, and deny any reports of such events related to MDMA misuse/abuse. Separate from this, a numerically higher incidence of substance use (apparently cannabis) was reported in the active MDMA arm (3 participants [6.5%] versus 0% in the placebo arm). Overall, the investigators concluded that MDMA did not exhibit abuse potential under the conditions within the trial.[32]

Refer to **Table 9** for a summary of non-psychiatric adverse events from the phase 3 trial. The first section reports AEs reported by the published article (Mitchell et al 2021), [32] and the second portion adds

additional non-psychiatric AEs for the same trial as reported on ClinicalTrials.gov. In some cases, discrepancies between the published report and ClinicalTrials.gov were noted.

Table 9. Non-Psychiatric Adverse Events of MDMA-assisted Therapy for PTSD from the Phase 3 Trial (NCT03537014)[32,50]

Non-psychiatric AEs	Active MDMA Number of affected patients (%)	Inert Placebo Number of affected patients (%)
Randomized: MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n = 45) *Safety Analysis: MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n =44)*		
TEAEs reported from the first MDMA/placebo dosing session to study termination[32]		
Abuse potential for MDMA (total)b	0 (0%)	0 (0%)
Blurred vision*	**4 (8.7%)**	**1 (2.3%)**
Cardiac events that may indicate QT prolongation (total)[c]	0 (0%)	1 (2.3%)
Chills*	**3 (6.5%)**	**0 (0%); or 9 (20.5%) per ClinicalTrials.gov[50]**
Decreased appetite*	**24 (52.2%)**	**5 (11.4%)**
Dry mouth*	**5 (10.9%)**	**2 (4.5%)**
Feeling cold*	**9 (19.6%)**	**3 (6.8%)**
Feeling jittery*	**5 (10.9%); or 6 (13.0%) per ClinicalTrials.gov[50]**	**0 (0%)**
Frequent urination*	**4 (8.7%)**	**1 (2.3%)**
Hyperhidrosis*	**9 (19.6%); or 10 (21.7%) per ClinicalTrials.gov[50]**	**1 (2.3%)**
Increased blood pressure*	**5 (10.9%); or 6 (13.0%) per ClinicalTrials.gov[50]**	**0 (0%)**
Irregular heartbeats and palpitations	0 (0%)	1 (2.3%)
Muscle tightness*	**29 (63%); or 30 (65.2%) per ClinicalTrials.gov[50]**	**5 (11.4%); or 6 (13.6%) per ClinicalTrials.gov[50]**
Muscle twitching*	**3 (6.5%)**	**0 (0%)**
Musculoskeletal pain*	**4 (8.7%)**	**0 (0%)**
Mydriasis*	**7 (15.2%)**	**0 (0%)**
Nausea*	**14 (30.4%); or 21 (45.7%) per ClinicalTrials.gov[50]**	**5 (11.4%)**
Non-cardiac chest pain*	**5 (10.9%)**	**1 (2.3%)**
Nystagmus*	**6 (13.0%)**	**0 (0%)**
Postural dizziness*	**6 (13.0%)**	**2 (4.5%)**
Pyrexia*	3 (6.5%)	1 (2.3%)
Somnolence*	**3 (6.5%); or 4 (8.7%) per ClinicalTrials.gov[50]**	**0 (0%)**

Table 9. Non-Psychiatric Adverse Events of MDMA-assisted Therapy for PTSD from the Phase 3 Trial (NCT03537014)[32,50]

Non-psychiatric AEs	Active MDMA Number of affected patients (%)	Inert Placebo Number of affected patients (%)
Substance use (cannabis)*	**3 (6.5%)**	**0 (0%)**
Urinary urgency*	**3 (6.5%)**	**0 (0%)**
Vomiting*	**4 (8.7%); or 5 (10.9%) per ClinicalTrials.gov[50]**	**0 (0%)**
Other AEs from baseline to study termination with incidence ≥ 5% reported on ClinicalTrials.gov[50]		
Abdominal discomfort	**6 (13.0%)**	**3 (6.8%)**
Arthralgia	5 (10.9%)	5 (11.4%)
Back pain	**7 (15.2%)**	**4 (9.1%)**
Crying	**0 (0%)**	**3 (6.8%)**
Diarrhea	4 (8.7%)	5 (11.4%)
Disturbance in attention	5 (10.9%)	6 (13.6%)
Dysmenorrhea	3 (6.5%)	1 (2.3%)
Dizziness	**11 (23.9%)**	**6 (13.6%)**
Ear pain	**3 (6.5%)**	**0 (0%)**
Fatigue	18 (39.1%)	16 (36.4%)
Feeling abnormal	3 (6.5%)	1 (2.3%)
Feeling body temperature change	**4 (8.7%)**	**1 (2.3%)**
Feeling cold	**9 (19.6%)**	**3 (6.8%)**
Feeling hot	4 (8.7%)	4 (9.1%)
Headache	**34 (73.9%)**	**25 (56.8%)**
Hypoesthesia	3 (6.5%)	2 (4.6%)
Influenza	**3 (6.5%)**	**0 (0%)**
Influenza-like illness	4 (8.7%)	4 (9.1%)
Jaw pain	4 (8.7%)	3 (6.8%)
Muscle spasms	3 (6.5%)	2 (4.6%)
Myalgia	3 (6.5%)	1 (2.3%)
Neck pain	3 (6.5%)	3 (6.8%)
Oropharyngeal pain	2 (4.4%)	3 (6.8%)
Pain	5 (10.9%)	5 (11.4%)
Palpitations	4 (8.7%)	6 (13.6%)
Paresthesia	6 (13.0%)	4 (9.1%)
Temperature intolerance	4 (8.7%)	2 (4.6%)
Tremor	**6 (13.0%)**	**3 (6.8%)**

Table 9. Non-Psychiatric Adverse Events of MDMA-assisted Therapy for PTSD from the Phase 3 Trial (NCT03537014)[32,50]

Non-psychiatric AEs	Active MDMA Number of affected patients (%)	Inert Placebo Number of affected patients (%)
Upper abdominal pain	**7 (15.2%)**	**4 (9.1%)**
Upper respiratory tract infection	6 (13.0%)	4 (9.1%)
Vertigo	3 (6.5%)	2 (4.6%)
Viral upper respiratory tract infection	**12 (26.1%)**	**6 (13.6%)**
Vomiting	**5 (10.9%)**	**0 (0%)**
Weakness (asthenia)	**7 (15.2%)**	**4 (9.1%)**

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PBO, inert placebo; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group.

*Indicates study authors considered the events as related to MDMA based on ≥2-fold incidence higher than placebo.

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] A classification used for any AEs using substance dependence-, addiction-, abuse-, overdose-, or diversion-related terms

[c] This is inclusive of multiple types of events, including irregular heartbeats/palpitations which is also reported separately

Summary Study Results for 6 out of 7 Phase 2 RCTs:

- The summary study compared the pooled active MDMA arm (initial dose of MDMA 75-125 mg) to control arms (initial dose of 0-40 mg MDMA) from phase 2 trials.[33]
- The most common non-psychiatric TEAEs (by System Organ Class) during the blinded study period at an incidence ≥5% among active participants versus control were gastrointestinal disorders (23.6% vs 6.5%). There was also numerically more participants with an eye disorder with active MDMA (6.9%) versus comparator (3.2%). Of note, there was not an increased incidence of infection or infestations with active MDMA (11.1%) compared to the comparator group (19.4%).[33]
- In general, investigators describe that most AEs were mild to moderate in severity, and often transient. An analysis of the frequency of AEs daily from the day of dosing to 7 days later supports the conclusion that the incidence of AEs tends to decline over 1 weeks after drug administration. Although these observations are only descriptive, AEs persisting among some active MDMA-treated participants on day 7 after dosing and numerically more frequently than control included, but were not limited to, lack of appetite, nausea, and dizziness.[33] Refer to **Appendix I Table I2** for the 7 day analysis summary.

- Summary safety results indicate that the most common (≥30% of participants) non-psychiatric TEAEs, reported more frequently in the active MDMA group on the day of the blinded experimental treatment sessions were dizziness, lack of appetite, nausea, muscle tension, perspiration, and sensitivity to cold. In contrast, a higher prevalence of fatigue, headache, and the need for more sleep was reported in the control arm compared to the active MDMA arm.[33]

Refer to **Table 10** for a summary of expected non-psychiatric AEs reported during blinded experimental sessions from the summary study of 6 phase 2 trials.

Table 10. Non-psychiatric Adverse Events from a Summary Study[a] (Mithoefer 2019[33]) of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD (NCT00090064; NCT00353938; NCT01958593; NCT01211405; NCT01689740; NCT01793610)

Non-psychiatric AEs	Active MDMA (Initial Dose of 75-125 mg) Number of affected patients (%)	Control (Initial MDMA Dose of 0-40 mg) Number of affected patients (%)
Randomized and Safety Analysis: MDMA 75-125 mg (n=72) for 2 sessions vs Control (MDMA 0-40 mg) (n=31)		
Expected reactions[b] reported during blinded experimental sessions 1 and 2		
Diarrhea	2 (2.8%)	0 (0%)
Dizziness	**29 (40.3%)**	**6 (19.4%)**
Drowsiness	10 (13.9%)	4 (12.9%)
Dry mouth	14 (19.4%)	5 (16.1%)
Fatigue	**35 (48.6%)**	**18 (58.1%)**
Headache	**38 (52.8%)**	**22 (71.0%)**
Heavy leg	**9 (12.5%)**	**0 (0%)**
Impaired gait/balance	**18 (25.0%)**	**3 (9.7%)**
Impaired judgment	0 (0%)	0 (0%)
Lack of appetite	**35 (48.6%)**	**7 (22.6%)**
Muscle tension	**27 (37.5%)**	**8 (25.8%)**
Nausea	**29 (40.3%)**	**6 (19.4%)**
Need more sleep	**7 (9.7%)**	**7 (22.6%)**
Nystagmus	**9 (12.5%)**	**0 (0%)**
Paresthesia	**9 (12.5%)**	**1 (3.2%)**
Perspiration	**24 (33.3%)**	**3 (9.7%)**
Sensitivity to cold	**28 (38.9%)**	**6 (19.4%)**
Thirst	**18 (25.0%)**	**2 (6.5%)**
Weakness	**7 (9.7%)**	**1 (3.2%)**

Table 10. Non-psychiatric Adverse Events from a Summary Study[a] (Mithoefer 2019[33]) of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD (NCT00090064; NCT00353938; NCT01958593; NCT01211405; NCT01689740; NCT01793610)

Non-psychiatric AEs	Active MDMA (Initial Dose of 75-125 mg) Number of affected patients (%)	Control (Initial MDMA Dose of 0-40 mg) Number of affected patients (%)

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] Participants that reported an expected, spontaneously reported AE during the experimental dosing session when active MDMA or control was administered.

3.7.4 Vital Sign Changes

Phase 3 trial

- Systolic and diastolic blood pressure and pulse transiently increased in the MDMA arm compared to the inactive placebo arm during the experimental sessions.[32]
- Two participants in the MDMA arm experienced transient increases in body temperature to 38.1°C (100.5°F): one participant experienced the event after the second experimental MDMA session, whereas the other participant experienced the event after the second and third experimental MDMA sessions.[32]

Summary Study Results for 6 out of 7 Phase 2 RCTs

- A dose-dependent effect with MDMA was observed for mean vital sign changes during sessions when MDMA was administered. Participants that received an active dose of MDMA (initial dose of 75−125 mg) tended to experience higher increases in mean systolic and diastolic blood pressure and heart rate compared to participants that received lower doses of MDMA (initial dose of 0-40 mg) or inactive placebo. However, by the end of the session, vital sign measurements trended down or returned to baseline values, suggesting the effect was transient. These averages were calculated based on vital sign measurements in 15-30 minute intervals during the 6-8 hour drug dosing sessions.[33]
- Body temperature showed a similar effect trend to vital signs, with transient increases observed in participants that received active MDMA versus participants that received the control. These averages were calculated based on vital sign measurements in 60 to 90 minute intervals during the 6-8 hour drug dosing sessions.[33]

Refer to **Table 11** for a summary of the vital sign and body temperature changes that occurred before and after MDMA administration during the experimental sessions, as reported by the summary study of 6 phase 2 trials.

Table 11. Vital Sign Changes During MDMA-assisted Therapy for PTSD from the Summary Study[a,b] (Mithoefer 2019[33]) of Phase 2 Trials (NCT00090064; NCT00353938; NCT01958593; NCT01211405; NCT01689740; NCT01793610)

Vital sign measurement timepoint	Active MDMA (Initial Dose of 75-125 mg) Mean (SD)	Control (Initial MDMA Dose of 0-40 mg) Mean (SD)
Randomized and Safety Analysis: MDMA 75-125 mg (n=72) for 2 sessions vs Comparator (MDMA 0-40 mg) (n=31)		
Systolic Blood Pressure (mmHg)		
Pre-drug	124.8 (15.9)	117.9 (11.7)
Peak	**150.6 (19.1)**	**132.6 (13.4)**
Final	125.2 (15.4)	117.7 (13.0)
Diastolic Blood Pressure (mmHg)		
Pre-drug	79.1 (10.4)	74.2 (8.2)
Peak	**91.3 (11.4)**	**84.5 (8.2)**
Final	77.8 (10.1)	73.2 (9.2)
Pulse (BPM)		
Pre-drug	73.4 (13.8)	69.2 (13.3)
Peak	**101.3 (17.6)**	**81.7 (15.6)**
Final	84.2 (15.1)	72.0 (13.4)
Body Temperature (°C)		
Pre-drug	36.4 (0.6)	36.3 (0.5)
Peak[b]	37.2 (0.5)	37.0 (0.5)
Final	36.8 (0.6)	36.7 (0.5)

Abbreviations: BPM, beats per minute; C, Celsius; MDMA, 3,4-methylenedioxymethamphetamine; mmHg, millimeters of mercury; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder; SD, standard deviation

Bold text indicates a statistically significant difference between the active MDMA arm and the control arm

[a] This information was accompanied by a hypothesis test in the summary publication, but without appropriate meta-analytic techniques, the statistical comparisons are uninformative.
[b] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the original amount.

3.7.5 Descriptive Safety Information at Long-term Follow-up

Descriptive long-term follow-up (LTFU) safety information for a subset of participants from phase 2 trials (n=91, about 87% of the total study population) at primarily 12 months after trial completion was published by Jerome et al. Suicidality assessed by the C-SSRS was stable or improved at LTFU; at baseline 60% of participants reported suicidal ideation and 1.5% reported suicidal behaviors, and at LTFU, 24% reported positive ideation and 0% reported suicidal behavior since the end of the trial. Self-reported

substance use indicated variable changes in alcohol use, cannabis use, and MDMA use since trial completion (ie, some with increased use, some with decreased use). LTFU participant-reported questionnaire responses indicated that 7 participants (8.6%) reported a harm from MDMA-assisted therapy including 2 participants (3.1%) with persistent harm at LTFU. Harms reported were considered mild-moderate in severity; variable types of harms were reported including changes in PTSD symptoms and others. The most common persistent harms reported were worsened mood (n=3, 3.6%) and other harms (n=3; 4.8% using denominator from 4 trials).[67]

3.7.6 Recommendations for Managing Safety Risks

According to the MAPS investigator's brochure published in March 2022, no MDMA-associated risks were considered to be 'High Level' (most serious designation). Cardiovascular and psychological risks were considered to be 'Medium Level', and other risks (ie, thermoregulatory, osmoregulatory, genotoxicity, reproductive) were considered 'Low Level.' Low Level risks were those that do not require new/special risk mitigation strategies. MAPS considers the overall risks of MDMA use to be low when it is administered in single divided doses for up to 3 times per treatment course, and in a controlled setting like that used in their clinical trials.[31]

The following is a summary of their recommendations for managing MDMA safety risks (note that this advice is intended for clinical trial investigators, but may also apply to MDMA use in non-trial settings):

- **General risk management:** Participants at higher risk for MDMA-assisted toxicities (eg, unstable cardiovascular disease, severe non-PTSD psychiatric condition) were excluded from the completed phase 3 trial.[63] Additionally, therapists and site physicians were accessible by phone for any issues during the study.[31]
- **Cardiovascular/sympathomimetic effects:** Transient increases in blood pressure and heart rate may occur; these changes usually resolve within 6 hours of ingesting MDMA. According to MAPS, for most individuals, these changes did not exceed values that are typically observed with moderate exercise. MDMA-induced prolonged QT interval was considered unlikely. Among MDMA-exposed participants (n = 358 in MAPS-sponsored trials as of March 2022), one participant experienced a serious adverse event of worsening of a cardiovascular condition (exacerbation of ventricular extrasystoles); the participant returned to baseline function after withholding additional MDMA doses and hospitalization for observation.[31]
    - Clinical trials excluded high-risk patients such as those with "…pre-existing cardiovascular disease, cerebrovascular disease or uncontrolled hypertension…" (page 146 of the Investigator's Brochure).[31] Note that the excluded populations included people with pre-existing arrythmias, and people with QT interval prolongation at baseline. Investigators could also exclude participants if they were considered to be at risk from the sympathomimetic effects.[32]
    - Monitor BP and HR prior to, directly following ingestion of MDMA, and at completion of dosing sessions[31,60]
    - Sites where administration of MDMA occurred were prepared to respond to (including immediate treatment onsite, plus transfer to emergency care as indicated) rare potential cardiovascular or cerebrovascular crises[31]

- Participants with emergent medical complications (including but not limited to QT interval >450 ms or an increases of ≥ 30 ms from baseline) during a dosing session should discontinue MDMA treatment[31]

- **Psychologic effects:** MDMA may precipitate psychological distress. Suicidal ideation and behavior is a recognized risk among people living with PTSD; the therapeutic setting in clinical trials (ie, tapering of psychiatric medications) and trauma-focused psychotherapeutic method may elevate this risk. Nevertheless, MAPS reports a low incidence of serious suicidality that appears to not be higher with active MDMA versus control in their studies to date (3 serious suicidality events have occurred after receiving active MDMA that were not considered MDMA-related).[32] In the completed phase 3 trial, the incidence of psychiatric AEs was generally similar between MDMA- and placebo-treated participants with a few possible exceptions including insomnia, bruxism, restlessness, and intrusive thoughts that occurred at a numerically higher rate in the MDMA arm.[50] The majority of events were considered mild to moderate and transient. Treatment-emergent suicidality during the phase 3 trial was not increased with active MDMA; 3 serious suicidal events occurred among 2 participants, all in the placebo arm.[32] Although, a higher incidence of positive suicidal ideation occurred in the active MDMA arm versus control arm in the summary study of 6 phase 2 trials.[33]
  - Clinical trials excluded patients that might be more sensitive to "…potential destabilizing psychological distress"[31] such as psychotic disorders or bipolar disorder type 1 (page 151 of the investigator's brochure)
  - Appropriate preparation of participants prior to MDMA dosing sessions (eg, preparatory therapy sessions, establishment of an appropriate trusting atmosphere and setting)[31]
  - Appropriate monitoring (ie, overnight stay at the study site the night of the dosing session, phone follow-up in the week following the dosing session, integrative therapy visits)[31]
    - Note that MAPS is evaluating the necessity of overnight stays following dosing sessions[***].[60] The completed phase 3 clinical trial required the majority of participants to stay overnight with monitoring by a trained attendant.[60]
  - Sites were prepared to respond to respond to severe psychological distress (eg, agitation, anxiety, suicidal behaviors).[32]
    - Distress present at the end of dosing sessions required a therapist or other team member (eg, nurse, attendant) to stay with the participant until it resolved or until the integrative appointment the next morning; daily follow-up with the therapists until stabilization was required. Severe distress responsive to sedatives (eg, panic attacks, insomnia) could be treated by lorazepam or a sedative-hypnotic (eg, zolpidem).[32] The phase 3 trial publication did not report the frequency of use of these agents.[32] We are aware of at least one phase 2 trial (also comparing active MDMA-assisted therapy to inert placebo-assisted therapy) that reported on use of these rescue medications. Overall, frequent and similar use of zolpidem

[***] *The completed phase 3 trial (Mitchell et al 2021) included a sub-study to investigate the necessity of overnight stays following dosing sessions (results are unknown to the writers of this report, though Mitchell et al reported that MDMA benefits were not changed by overnight stay without additional detail). Participants in this sub-study had to have stable home environments, and have a vetted support person aware of how to respond to participant distress with them at home. Therapists contacted the participants at home that night and were available by phone.*

occurred after MDMA-assisted sessions compared to therapy-only sessions (60.7% versus 68.8%, respectively; P=0.77). Similarly, benzodiazepine use occurred after 47% of MDMA-assisted sessions and 37% of therapy-only sessions (P=0.57). Investigators described that many participants requiring these breakthrough medications were taking them prior to the trial.[33]

- Suicidality was closely monitored in MAPS-sponsored studies using the C-SSRS, and general monitoring by therapists. Of note, participants with a history of suicidality were not excluded from participation unless they were considered to have high active risk at baseline.[32]

- **Thermoregulatory effects:** Compared to placebo, more active MDMA-treated participants experienced body temperature increases >1°C above baseline. MAPS states that the room where MDMA is administered should be kept at a comfortable temperature; if the participant feels hot, steps should be taken to lower their temperature (eg, use of a fan, removal of extra clothing layers). A physician should evaluate any body temperature increase of ≥ 1.5°C from baseline.[32]
- **Osmoregulatory effects:** During dosing sessions, management of participant fluid intake was required. MAPS instructs that participants should not ingest >3L of water, and recommends spreading out the water intake (ie, over the ≥ 8 hours). Suspected dilutional hyponatremia or other osmoregulatory toxicity should result in holding any further MDMA doses.[32]
- **Genotoxicity effects:** MAPS does not consider MDMA to have genotoxicity risks based on negative *in vitro* and *in vivo* tests.[32]
- **Reproductive effects:** There is a lack of information about use of MDMA in pregnant people. According to MAPS, epidemiological studies in people have shown mixed results; some (examining MDMA [as Ecstasy] and polydrug use) have shown abnormalities at birth. Their overall assessment of available clinical data and animal studies suggest that a negative impact of MDMA on embryo-fetal outcomes during early pregnancy or male fertility is unlikely. Participants who could become pregnant during the MDMA clinical trials were required to use effective contraception until 10 days after the last dose of MDMA.[32]
- **Other effects (considered to be 'Minimal Risks' or unclassified level of risk):**
  - *Common AEs:* Common AEs that have occurred during MDMA dosing sessions were usually temporary and self-limiting, resolving within approximately 48 hours of taking MDMA. In the placebo-controlled phase 3 trial (page 153 of the Investigator's Brochure):

    "…the most common adverse events reported more frequently in the MDMA group were (>20%) muscle tightness, decreased appetite, nausea, hyperhidrosis, feeling cold, (>10%) restlessness, mydriasis, dizziness (postural), bruxism, nystagmus, increased blood pressure, feeling jittery, chest pain (non-cardiac), dry mouth, vision blurred, pollakiuria, intrusive thoughts, vomiting, stress, and musculoskeletal chest pain."[32]
  - *Neurotoxicity:* Existing evidence using the MAPS-sponsored MDMA-assisted therapy dosing regimen do not support a lasting negative impact of MDMA on participant cognition. Likewise, other nonclinical and toxicokinetic evidence have not demonstrated neurotoxicity.[32]
  - *Abuse potential:* MAPS suggests that MDMA possesses moderate abuse potential that is of lower risk than stimulatory drugs of abuse (eg, cocaine). Under the conditions used in MAPS-sponsored MDMA studies, they have not observed AEs related to the potential for MDMA

abuse. They point out that epidemiologic studies of people taking MDMA in any setting report that a small percentage of people, especially populations considered to be most vulnerable to substance abuse, may develop problematic MDMA use.[31] Note, though, that some higher-risk participants (eg, current alcohol or drug abuse) were excluded from the completed phase 3 trial.[63]

- *Immunological effects (MAPS did not explicitly classify the level of this risk):* Like other medications with serotonergic effects, MDMA (at a dose of 100 mg) has been observed to induce immunosuppressive changes lasting approximately 24 hours.[31] The phase 3 clinical trial publication does not discuss infections, though per reporting on ClinicalTrials.gov for that trial, the proportion of participants in the active MDMA arm with an upper respiratory tract infection (13.4%), viral upper respiratory infection (26.1%), or influenza (6.5%) was numerically higher than those in the placebo arm (9.1%, 13.6%, and 0%, respectively).[50†††]
- *Hepatic Effects (MAPS did not explicitly classify the level of this risk):* MAPS studies among participants without PTSD, and studies among people with PTSD generally have not supported MDMA-induced hepatotoxicity. Though, a summary study of healthy participants found a statistically significant change in gamma-glutamyl transpeptidase, but not other measures (eg, ALT or AST). In the investigator's brochure on page 149, MAPS concluded that "…on average, MDMA does not influence hepatobiliary function in most people, however there is evidence of a rare idiosyncratic hepatotoxicity."[31]
- *Major morbidity or mortality in epidemiologic studies of MDMA (ie, including studies of Ecstasy) use:* The most commonly reported events observed are hyperthermia (and hepatotoxicity secondary to hyperthermia), psychiatric problems (eg, anxiety, panic attacks), and hyponatremia. Also, fatal dysrhythmias have been reported in association with MDMA use; people with underlying pulmonary and/or cardiac conditions (including Wolff-Parkinson-White syndrome, among others) may be at elevated risk for these serious events. Overall, MAPS considers these events to be rare relative to the total estimated prevalence of MDMA use worldwide, and are confounded by uncontrolled factors (eg, uncontrolled settings that may include polydrug use or MDMA of unknown purity). MAPS investigators suggest that the controlled setting for MDMA-assisted therapy may mitigate many of these risks.[31]

3.8 Risk of Bias Assessment

3.8.1 Bias Threats in Psychedelic Drug Trials

There are established challenges to designing and conducting psychedelic drug (ie, including medications like MDMA) trials. In a 2022 recent review article, Aday et al pointed out multiple threats to measuring a true treatment effect. Three major challenges included selection of a comparator, maintenance of blinding, and prevention of expectancy effects (ie, a participant's expected outcome of treatment, positive or negative). Some suggestions to minimize these effects according to Aday et al are 1) using active placebo comparators, 2) excluding participants with prior exposure to the experimental drug or comparator, 3) using neutral tones about efficacy and possible adverse events during participant

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††† *Of note, the MDMA Investigator's Brochure stated different percentages for the rate of upper respiratory tract infections (it reports 26% of MDMA participants versus 22% of placebo participants).*

recruitment, 4) measuring expectations before treatment and treatment group allocation guesses after treatment, and 5) incorporating expectancy effect and blinding efficacy measures into the data analysis.[68] (This is not a comprehensive list of recommendations; refer to Aday et al 2022 figure 3 for all recommendations). Notably, many of these suggestions may be underreported or underexplained in results by investigators if they were used, limiting the ability of readers to fully interpret possible bias.

It is also important to recognize that these issues are complex, and even if there is an agreed approach for minimizing the impact of these effects, scientists may disagree on how to interpret the information. For example, while testing blinding efficacy (eg, asking participants to guess which treatment they received at the end of a blinded trial) is a suggested approach to gauge the effectiveness of blinding, some have pointed out that a correct guess does not conclusively indicate that unblinding occurred.[68] The Cochrane Collaboration points out that correct guesses are more likely to occur when there are marked differences in efficacy or adverse events between trial groups. And, a correct guess does not necessarily increase bias in the trial.[41]

Also, as a reminder, our assessment of bias was limited to the blinded period of trials that included a control arm. The phase 2 trials also included additional open-label follow-up during which some participants from the control arm were permitted to receive full-dose MDMA-assisted therapy.[33,43] We did not consider this follow-up period in our assessment, although we recognize that performance bias could be introduced by therapist/participant awareness of treatment group allocation.

3.8.2 Summary of Risk of Bias (ROB) Assessment

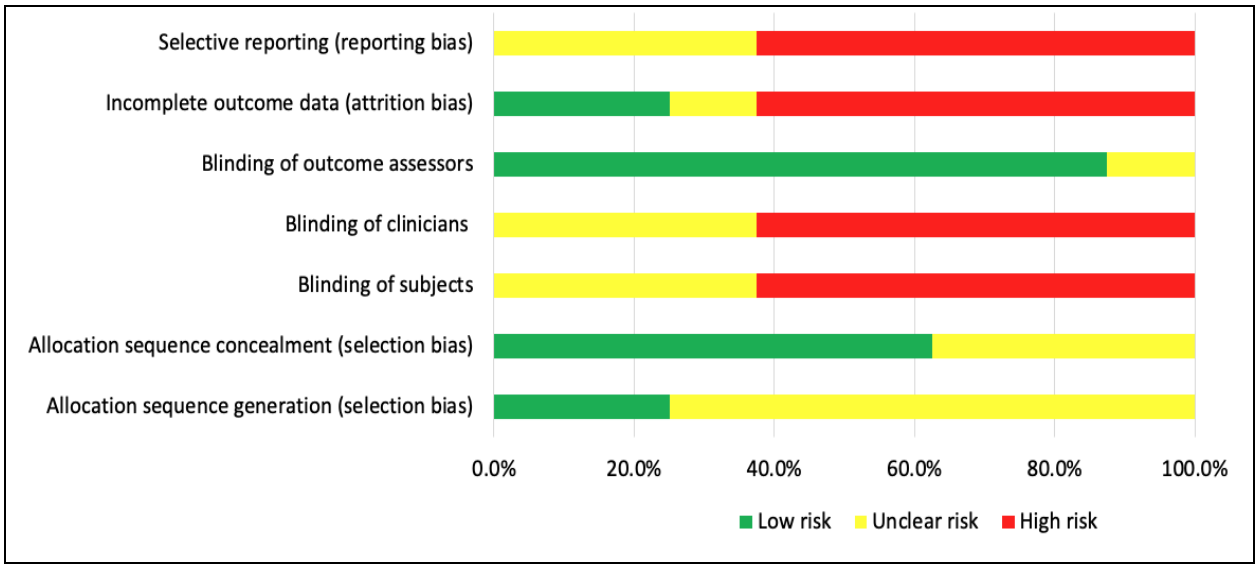
We used a domain-based approach by Page et al to assess bias threats arising from known threats to the internal validity of RCTs.[36] **Figure 1** summarizes the percentage of included RCTs assessed as low risk, unclear risk, or high risk for each part of this assessment. Most trials (7/8, 87.5%) were rated as high risk for at least 1 component.[32,43,45-49] Only the ROB factors of random sequence generation, allocation concealment, and blinding of outcome assessors lacked a high-risk rating.

Random sequence generation and allocation concealment:

- All 8 RCTs were considered to have a low (25%) or unclear ROB (75%) arising from randomization and allocation concealment (62.5% low and 37.5% unclear).[32,43-49]

Blinding of participants, personnel, and outcome assessors:

- A higher ROB was found due to a risk of unblinding of participants and personnel despite the fact that nearly all trials attempted blinding: 62.5% were considered to be high risk,[32,45-47,49] and the remaining trials were rated as unclear risk (37.5%).[43,44,48] None were considered to be low risk.
- In contrast, the factor rated as having the lowest ROB among the 8 RCTs was blinding of outcome assessors. Nearly all (87.5%) trials were considered low risk for blinding of outcome assessors since they reported using independent outcome raters that did not observe any of the experimental dosing sessions that might unblind the outcome assessor from the subjective/expressed effects of MDMA during the dosing session.[32,46-49,51,59]



Abbreviation: RCT, randomized controlled trials; ROB, risk of bias.

[a] Figure based on categories of bias from the Cochrane Collaboration[69]

Figure 1. Percentage of RCTs with Low, Unclear, or High ROB, per the Domain-based ROB Approach[a]

Incomplete outcome data (attrition bias):

- Over half (62.5%) of the trials were rated as being high risk,[32,43,46,48,49] whereas 25% were rated as low risk.[44,45]
- Most of the cases judged to be high risk for attrition bias were either due to overall high attrition rates (ie, >5%), which is particularly apparent with the low sample sizes, or due to lack of clarity in reporting reasons that participants were excluded (eg, 'subject withdrawal').

Selective reporting bias:

- Over half (62.5%) of the trials were rated as being high risk for selective reporting owing to various discrepancies between reporting sources (ie, published journal article and ClinicalTrials.gov results for the same trial), or overt discrepancies between outcomes the investigators planned to collect by study protocol and the outcomes reported.[32,46-49]

Appendix J Table J1 shows our rating for each component by each trial, Jadad scores, and includes a rationale for the assigned level of risk.

It is important to point out that for **unpublished trials** (3 of 8 included RCTs),[43-45] we were limited to information reported on ClinicalTrials.gov and the trial protocol, if available. For this reason, many domains for unpublished trials are rated as having an unclear bias risk from lack of information. Keep in in mind that there are other inherent concerns with unpublished trials that may not be addressed by the domain-based approach. For example, unpublished trial methods and results have not been peer-reviewed for a journal. Also, 2 of the unpublished trials (NCT00402298 and NCT019958593) were terminated early, apparently for reasons unrelated to efficacy or safety, which limits the interpretability of their results.[43,44] Per the trial investigators, the quality of the data reported by one of these trials (NCT00402298) cannot be guaranteed.[43]

The domain-based ROB assessment was supplemented with calculating the Jadad score; higher Jadad scores indicate less potential for bias (the maximal score is 5).[42] Calculated Jadad scores for the 8 included MDMA-assisted therapy RCTs range from 2 to 5. Most of the trials received a low Jadad score: 3 (37.5%) of the trials were rated as a 2[43,45,46] and 4 (50%) were rated as a 3,[32,47-49] indicating some concerns. The lower Jadad scores were due to insufficient reporting of the exact method used to generate the allocation sequence (eg, use of a computer-generated, or truly random technique), concerns about the risk of unblinding (despite use of good blinding techniques), and incomplete outcome data for many trials. Despite not reporting of the exact method for randomization, most of the studies reported using a "randomization monitor" and hint that the sequence was randomly determined.[51,52,58,59] If we considered this to be sufficient, this would increase 4 (50%) of the Jadad scores by 1 point.

We also assessed for bias arising in adherence to or delivery of the trial intervention, and funding bias. Among the trials, 62.5% included information details about the participants dropping out of the trial,[32,46-49] from which we inferred the proportion of randomized participants completing all blinded dosing sessions for active MDMA or control. Of these, the approximate proportion of participants completing all planned blinded experimental sessions ranged from 88-95.6% for the active MDMA arms, and from 83-100% for the control arm.[32,46-49] There was insufficient information reported about "re-training" (ie, review/feedback on therapy technique) of therapists or fidelity of therapists to the MDMA-assisted therapy protocol. One unpublished trial (NCT01689740) included an open-label lead-in phase for the first 2 enrolled participants; during this time, 2 of the overall 3 therapist dyads providing therapy during the trial received feedback on their therapy to ensure the reliability and consistency of their approach.[51] This was the only trial that reported using an open-label lead-in phase to standardize therapy. Although, therapists without prior experience with the MDMA-assisted therapy technique may have completed a separate open-label lead-in phase according to the phase 3 study protocol.[60] Four trials (50%) reported plans to use trained "adherence raters" to assess fidelity to the therapeutic approach according to their trial protocol,[52,58,60] but only one trial reported any detail on this effort.[48]

Lastly, funding bias was assessed by collecting information about the study sponsor and their role in each study. All trials were funded by the non-profit organization, Multidisciplinary Association for Psychedelic Studies (MAPS)[43]; one study also had a co-sponsor, the Swiss Medical Association for Psycholytic Therapy.[48] The MAPS organization or MAPS employees were involved in various steps from study conduct to reporting for each of the included trials, except for one with insufficient information to assess MAPS's role.[43] Additionally, published studies reporting competing interests among authors reported that most non-MAPS employee authors received MAPS funding for conduct of the current study or other roles. The significance of MAPS's role in conduct of these studies is unclear. Refer to **Appendix J Table J2** for a summary of adherence ratings, and assessment of funding bias for each trial.

A limitation of our bias assessment is that our approach did not consider validity of the outcome measures used. The primary efficacy outcome for each trial used the clinician-administered PTSD tool for diagnosing PTSD and assessing its severity either according to the DSM-IV (CAPS-4), or the most recent DSM-V (CAPS-5). Both of these tools have been psychometrically validated[64,66,70] and appear to have been used by the trials in a way consistent with their original purpose.

3.8.3 Discussion about Major Bias Threats among MDMA-assisted Therapy for PTSD RCTs

Below is a discussion about the biggest bias threats identified by our assessment:

Unblinding of treatment allocation. Notable physiologic (ie, transient increases in blood pressure and heart rate) or subjective changes associated with MDMA increase the risk of unblinding. Prior exposure to MDMA may also increase the risk of unblinding.[68] In the phase 3 trial, 32% of participants overall (39% in the MDMA arm and 25% in the placebo arm) reported a lifetime history of MDMA exposure.[32] Use of a comparator with greater similarity (eg, low-dose MDMA used in some of the phase 2 trials) minimizes this risk,[68] but may not eliminate it. Collecting participant/therapist guesses on allocated groups may help readers interpret blinding success (with limitations as noted above). Treatment allocation guesses (participant and/or therapists) were reported by 5 of 8 of the trials.[32,46-49] The proportion of correct guesses was variable among the trials (see **Appendix J Table J1**). The 2 trials that used an inert placebo and reported guesses, which includes the phase 3 trial, reported the highest rates of correct guesses: 95% in the phase 2 trial (Mithoefer et al 2011)[49] and 90% in the phase 3 trial.[32] One phase 2 trial using a low-dose MDMA comparator (Oehen et al 2013) concluded that blinding was likely adequate since 59% of guesses were correct (66% correct for the active MDMA dose and 46% for the low-dose MDMA), which was considered close enough for any differences to be attributable to chance.[48]

MAPS investigators did utilize blinded efficacy outcome assessors that did not observe MDMA-assisted therapy sessions and thus were more likely to maintain blinding. Blinding of the outcome assessors does mitigate bias in the measurement of the efficacy outcome, but does not eliminate possible bias arising from the participants or therapist knowledge of their treatment allocation. For example, in a critique of the phase 3 trial by Mitchell et al, Burke and Blumberger point out that unblinding of participants leads to an unequal distribution of placebo (ie, anticipated positive effect) and nocebo (ie, anticipated negative effect) effects across the active MDMA and control arms.[71] The possible unequal distribution of the placebo and nocebo effects between active and inactive treatment arms could introduce confounding bias that favors observing higher efficacy with active MDMA versus control. Thus, there is uncertainty about whether the greater efficacy with active MDMA versus comparator is attributable to the medication or a boost from increased placebo effect in the active MDMA arm and greater nocebo effect in the control arm. Nonetheless, the consistency of a beneficial effect of MDMA-assisted therapy among most phase 2 and 3 trials, and the large treatment effect increases confidence in the direction of effect (ie, *improved* CAPS scores with MDMA treatment). There remains some uncertainty about the true magnitude of the effect size.

Attrition bias. Five of the RCTs were rated as being high risk for attrition bias.[32,43,46,48,49] In part, this was due to the relatively small sample size of most trials so that attrition of a small number of participants represented ≥5% of the study population. The phase 3 trial was rated as high risk for attrition bias owing to 8 (8.8%) of participants (4 participants in each treatment arm) reported as missing the visit when the primary endpoint was measured (T4), implying an unknown final outcome.[32] The statistical analysis model used for the efficacy analysis (mixed model repeated measures [MMRM] may yield reliable effect estimates when missing data can be considered missing at random (ie, any systematic differences between the collected and missing values can be predicted by other available variables).[72] The phase 3 trial statistical analysis plan described planning to conduct a sensitivity analysis to test the robustness of the missing at random assumption,[73] which is an approach that has been recommended in the

literature,[74,75] but as far as we can tell, the outcomes of the planned sensitivity analysis were not included in the published trial report. So, some uncertainty remains. We *estimate* that if the model could not robustly account for the missing efficacy outcome data, the treatment effect would tend to be overestimated,[74] favoring MDMA-assisted therapy.

Another consideration for the seriousness of bias arising from missing outcome data, is the *reason* for missing participant information. In the phase 3 trial, 4 participants in each arm (8 total) withdrew consent and missed the last outcome measurement.[32] Three additional placebo participants discontinued the intervention and had some missing data, but did not withdraw from the trial.[32] Of those withdrawing from the study, it is unclear if there was a pattern to the reason for discontinuation that differs between arms. Among the MDMA participants, 2 of 4 discontinued due to COVID infection (1 placebo participant also discontinued for this reason), 1 of 4 discontinued due to early benefit from treatment, and 1 of 4 due to PTSD symptoms triggered by the CAPS scale/depressed mood. [32] The remaining withdrawing placebo participants discontinued due to adverse events (insomnia and serious suicidal ideation) and participant's choice. For the additional 3 placebo arm participants who discontinued the intervention but remained in the trial for follow-up, the reason for intervention discontinuation included suicide attempt (1), COVID infection (1), or increased anxiety (1); these 3 participants along with the previously mentioned study withdrawals were not factored into the T4 *de jure* estimand primary outcome.[32] Overall, confidence in a true significant difference for the primary outcome by the phase 3 trial is somewhat bolstered by the large effect size, and consistency of the significant benefit of MDMA over placebo in multiple analyses (ie, the primary *de jure* analysis and sensitivity analysis with the *de facto* estimand, assessing treatment as allocated).[32] However, these analyses still suffer from similar possible limitations from the missing data, as discussed above.

Outcome reporting bias. Selective reporting is a reporting bias associated with exaggerated benefits of treatment based on presenting the most favorable outcomes or details.[76] We noted inconsistent reporting of 1 or more outcomes in 62.5% of the trials, [32,46-49] which may indicate selective reporting bias. Although these observations are considered high-risk using our ROB criteria, the impact on the overall assessment is uncertain. All trials consistently reported the planned primary efficacy outcome (ie, changes in CAPS scores) implying a lack of selectivity for this outcome. Some differences were found in reporting of adverse events between sources (ie, the published journal article versus ClinicalTrials.gov). [32,44,48,49] For the phase 3 trial, we noticed instances in which relatively frequent adverse events occurring numerically more with MDMA than placebo (eg, viral respiratory infections)[50] were not reported in the published article.[32] However, it is possible that some differences could be due to variation in the reporting period or the threshold for the percentage difference between study arms to be included in the publication. One phase 2 trial (Ot'alora 2018) reported planning to measure patient-reported PTSD symptoms using the Posttraumatic Diagnostic Scale (PDS),[58] but this outcome was not reported in the publication or on ClinicalTrials.gov.[46,52]

Adherence and treatment fidelity. Reporting of the proportion of participants completing all MDMA/comparator-assisted sessions varied among studies. The majority of included trials reported when participants discontinued trials, but this did not necessarily describe whether participants missed experimental or other therapy sessions. In the phase 3 trial, 91% of MDMA participants and 84% of placebo participants completed all 3 experimental dosing sessions.[32] We also attempted to assess therapist fidelity to the non-directive MDMA-assisted therapy protocol. Only 2 phase 2 trials reported some information about ensuring therapist fidelity: one of these used an open-label lead-in period to

ensure reliability and consistency for 2 of 3 of the trial therapist pairs,[45] and the other reported information about adherence raters.[48] Yet, according to trial protocols (available for all trials except for 2[43,48]), investigators did provide therapists with training on the therapeutic method and planned to assess fidelity to the approach using trained "adherence raters." The only trial hinting at results from adherence raters noted that the adherence raters (page 50 Oehen et al 2013) "…noticed a few areas where our therapy differed somewhat from the manual, in that our approach was considered more directive in some places."[48] The investigators then go on to point out "Whether this had any impact on the outcomes will require additional research."[48]

Assuming that the non-directive therapy is effective for treatment of PTSD, the biggest threat to bias arising from the delivery of the therapy is if therapist pairs delivered therapy differentially in a way that favors the MDMA arm, boosting its efficacy. The likelihood of this threat is unknown due to lack of information, but should not be ignored, particularly due to the high risk of unblinding of therapists after the first experimental dosing session. The phase 3 trial protocol notes on page 26 that "There will be separate, open-label, lead-in protocols following identical study procedures for new therapy teams to receive clinical supervision from the sponsor."[60] MAPS investigators published a report of therapist dyad adherence to MDMA-assisted therapy during 2 open-label trials preceding the phase 3 trials.[77] It is not clear, but these could possibly be the open-label lead-in periods referenced by the phase 3 trial protocol. The purpose of conducting the open-label phase 2 trials was to demonstrate the consistency and scalability of the approach across multiple sites, to support the phase 3 trial. Results from this study demonstrated relatively high adherence scores by the 37 therapy teams (mean 95% adherence; standard deviation 3.7%).[77] While this may slightly bolster confidence in the ability to deliver a consistent approach by a large number of therapist teams, there remains insufficient information to assess delivery during the blinded RCTs.

4.0 SUMMARY

Results from 5 of the 7 included phase 2 trials (n=99)[45-49] and 1 phase 3 RCT (n=91)[32] found that 2 or 3 MDMA-assisted therapy sessions, separated by 3-5 weeks and using an oral divided dose of MDMA 80-187.5 mg in combination with 29-40 hours of non-directive manualized therapy, tended to favor or significantly reduced moderate to severe PTSD symptoms after short-term (1-2 month) follow-up. Relative to the control (low-dose 'inactive' MDMA or inert placebo with matched psychotherapy), the effect size of MDMA-assisted therapy on the change in PTSD symptoms from baseline to 3-8 weeks after the last dose was large, 0.9 by Cohen's *d,* in the phase 3 trial.[32] Descriptive statistics of clinically important outcomes including the loss of a PTSD diagnosis, PTSD remission, or ≥30% improvement in PTSD symptoms also support the short-term efficacy of MDMA-assisted therapy. In the largest phase 3 trial, a higher proportion of active MDMA participants (67%) no longer met PTSD diagnostic criteria 8 weeks after the last MDMA dose than participants receiving inert placebo (32%).[32] Indirect comparison of effect sizes suggests that MDMA-assisted therapy may be at least similarly effective, or possibly superior, to first-line PTSD therapies including trauma-focused therapy, and possibly better than first-line SSRIs.[21] However, this should be confirmed by high-quality clinical trials given the potential inaccuracies of comparing the effect of different therapies studied under heterogeneous conditions.

Participants in MDMA-assisted therapy RCTs were adults (mean age around 40 years for many trials) with primarily severe PTSD at baseline.[32,33] Most participants also suffered from MDD with a high proportion having a *lifetime* history of suicidal ideation (92% in the phase 3 trial), serious ideation (41% in the phase 3 trial), or suicidal behavior (32% in the phase 3 trial).[32,33] All trials tended to enroll participants that were otherwise healthy, lacking other severe psychiatric illnesses, or severe or uncontrolled medical conditions. Many participants had received at least 1 other treatment for PTSD prior to the trial,[32,33] suggesting MDMA-assisted therapy may be an effective option for people failing first-line treatments. Trials also enrolled participants with diverse trauma histories,[32,33] supporting potential use of MDMA-assisted therapy for civilian and veteran populations. In the phase 3 RCT, preliminary evidence from 21% of participants with the difficult-to-treat dissociative PTSD subtype showed that MDMA-assisted therapy was similarly effective for people with and without dissociative PTSD.[32]

Adverse effects (AEs) occurring during RCTs were primarily considered mild to moderate in severity and transient.[32,33] Common psychiatric events considered to be possibly related to MDMA in the phase 3 trial were bruxism, restlessness, intrusive thoughts, nervousness, and stress.[32] Similar effects were observed among phase 2 trials, with increased anxiety, difficulty concentrating, jaw clenching, and low mood also occurring numerically more frequently with active MDMA than controls.[33] Common non-psychiatric events occurring more frequently with MDMA were relatively consistent between the phase 3 and phase 2 trials, including but not limited to, gastrointestinal effects (decreased appetite, nausea), muscle tightness, headache, dizziness, perspiration, and cold sensitivity.[32,33] For most people, MDMA-associated effects resolved within 7 days of MDMA administration.[33]

On the days of MDMA administration, transient increases in systolic and diastolic blood pressure and heart rate were observed.[32,33] These effects occurred consistently between different dosing sessions, and the mean changes returned to baseline by the end of 6-8 hour sessions.[33] MAPS describes the physiologic changes as being no different than the peak effects of moderate intensity exercise for most

people.[31] However, participants with severe cardiovascular disease, which were excluded from MDMA-assisted therapy RCTs,[32,33] may be more sensitive to these changes, as well as other acute sympathomimetic MDMA effects.

In contrast, participants in the control arms had greater persistence of moderate-severe PTSD symptoms, and more placebo arm participants in the phase 3 trial experienced psychiatric AEs of anxiety, irritability, nightmares, suicidal ideation, and intentional self-injury than in the MDMA arm.[32] Reported non-psychiatric events tended to be more frequent with MDMA-assisted therapy, although chills and crying were numerically more frequent in the placebo arm.[32]

Regarding serious adverse events during the RCTs, no deaths were reported per ClinicalTrials.gov,[43-45,50,52,53,55] and none of the SAEs occurring in the active MDMA arm during the blinded trial period were considered to be MDMA-related by the investigators.[46-49] One SAE of exacerbation of ventricular extrasystole during an open-label MDMA (125 mg) session that resolved after hospitalization for observation with no apparent sequelae was considered possibly MDMA-related.[33,47] In the phase 3 trial, suicidality was not increased with MDMA (6.5%) compared to placebo (11.4%).[32] However, the summary study of 6 phase 2 trials found a transient increase in suicidal ideation among people receiving active MDMA versus control. Yet, investigators point out that there was a greater incidence of suicidal ideation among active MDMA participants at baseline, so there is uncertainty about whether the increased suicidal ideation is due to MDMA.[33] The phase 3 trial reported a lack of cases of MDMA abuse.[32]

The risk of bias (ROB) assessment found that none of the 8 RCTs were considered low risk for all factors assessed. Most (62.5%) of the trials were considered high-risk due for potential unblinding of participants and personnel to treatment allocation, as knowledge of treatment allocation could inflate the benefits of MDMA over placebo due to changes in patient or therapist behavior. Trials did attempt to blind participants and therapists, but reports of patient and/or therapist guesses of the assigned allocation suggest that blinding was unsuccessful in many cases. For example, in the phase 3 trial, about 90% of participants correctly guessed their assigned treatment.[32] Maintenance of blinding is a recognized challenge for clinical trials of psychedelic medications.[68] Blinding of outcome assessors, which was performed by each RCT, may mitigate bias in the collection of the outcome, but does not eliminate possible bias arising from unblinding of participants and/or personnel.

In addition, 5 of the 8 RCTs were rated as being high risk for attrition bias. In part, this is due to the small sample size of most trials so that attrition of a small number of participants represents ≥5% of the entire population. The phase 3 trial was rated as high risk for attrition bias due to missing outcomes. Although the statistical analysis may provide reliable estimates when certain assumptions about the missingness of the data are met, there is uncertainty about whether the assumptions were met. This concern was compounded by discrepancies in the details about handling of the missing outcomes in various analysis conducted and the lack of reported sensitivity analysis about the missing data assumption. Overall, we estimate that if present, attrition bias may overestimate the efficacy of treatment and underestimate possible harms of treatment.

Finally, we noted inconsistent reporting of 1 or more outcomes in 62.5% of the trials, which may indicate selective reporting bias. Although these observations are considered high-risk using our ROB criteria, the impact on the overall efficacy assessment is uncertain. All trials consistently reported the planned primary efficacy outcome (ie, changes in CAPS scores) implying a lack of selectivity for this outcome. Some differences were found in reporting of adverse events between sources (ie, the

published journal article versus ClinicalTrials.gov). However, it is possible that some differences could be due to variation in the reporting period or the threshold for the percentage difference between study arms to be included in the publication.

Three small phase 2 RCTs were not published in a journal.[43-45] Thus, results of these trials have not been peer-reviewed. Notably, 2 of the 3 trials were discontinued early after enrolling only a fraction of the planned number of participants.[43,44] The reason for early discontinuation does not seem to be related to MDMA treatment. One of the discontinued trials cited personnel turnover as the reason for early termination; on ClinicalTrials.gov, the sponsor notes that the quality of data from this trial cannot be guaranteed.[43]

5.0 OVERALL CONCLUSION

Evidence from 1 phase 3 randomized controlled trial (n=90) supports MDMA-assisted therapy as an effective option for people with chronic, severe PTSD.[32] The phase 3 trial results are supplemented by 7 small phase 2 trials among people with moderate to severe, chronic PTSD.[43-49] Available evidence is most applicable to people with severe PTSD that have failed at least 1 first-line PTSD treatment and lack severe medical comorbidities. The phase 3 trial included participants with dissociative PTSD, and preliminary evidence suggests MDMA-assisted therapy is at least similarly effective in this subpopulation.[32] Many participants in the phase 3 trial also had MDD with a lifetime history a suicidal ideation.[32] Trials also enrolled participants with diverse trauma histories, supporting potential use of MDMA-assisted therapy for civilian and veteran populations.[32,33] Few people included in RCTs were diagnosed as having moderate PTSD symptoms at baseline,[33] though there is an ongoing phase 3 trial evaluating MDMA-assisted therapy for this population.[61] Limitations of the available RCT evidence are the relatively small sample size, homogenous population, and the possibility of an overestimate of benefits and underestimate of risks, primarily due to possible attrition bias and confounding bias from unblinding of participants and therapists to treatment allocation. It is important to keep in mind that the evidence reviewed for this report is limited to the MAPS-sponsored formulation of MDMA, and the evidence in favor of safety of efficacy may or may not extend to other MDMA formulations.

Safety information from relatively short-term (maximum of approximately 12 months) follow-up have not demonstrated an increased risk of severe adverse events for most participants.[32,33] Though, enrolled participants were at lower risk for severe adverse events based on the absence of psychotic disorders, active substance use disorders (exceptions were mild disorders, moderate disorders in early remission or cannabis use disorder),[78] and uncontrolled or severe cardiovascular disease at baseline.[32,33]

Delivery of MDMA-assisted therapy using the model from the phase 3 RCT requires at least 2 trained therapists (eg, having at least a master's degree and trained on the MDMA-assisted therapy model) for each person receiving the treatment. To complete MDMA-assisted therapy as studied in the phase 3 trial, the therapists and participants must be available for approximately 15 therapy sessions totaling over 40 hours.[32] Additionally, close monitoring for psychiatric and medical adverse events in a safe, controlled setting is required during the MDMA-assisted therapy sessions.[60] In clinical trials, most participants stayed with an attendant at the treatment facility the night after receiving MDMA.[32]

The non-profit organization sponsoring these trials, MAPS, hopes to submit evidence for approval of MDMA-assisted therapy for PTSD to the FDA in 2023 once top-line results from the second phase 3 trial are available.[23] If successful, it is projected that FDA approval could be granted around May 2024.[24]

The overall body of evidence reviewed by this report supports a significant benefit from MDMA-assisted therapy for severe chronic PTSD. However, the direction of potential biases tends to be nonconservative, meaning that it is likely that the magnitude of the efficacy estimate is overestimated, and that risks are underestimated. Relative consistency of the benefits of MDMA-assisted therapy across the included RCTs and the large treatment effect size decreases the likelihood that the biases could be explaining all of the benefit, but there is greater uncertainty about potential risks. Results of additional well-designed trials, and longer follow-up, could improve our understanding of the magnitude of benefit and risks of treatment. However, particularly due to the recognized challenges of conducting trials with psychoactive drugs, some biases (eg, performance bias from unblinding) may be difficult to eliminate completely. Quantitative synthesis, also including possible meta-regression, could improve our understanding of uncertainty in the current evidence. For example, it would allow greater precision in estimating safety outcomes, and enable examination of the impact of other factors (eg, blinding, MDMA dosages) on the outcomes.

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APPENDIX A – LITERATURE SEARCHES

The tables below show phase 2 searches in the CENTRAL database and PsycINFO database via EBSCOhost.

Table A1. CENTRAL Search for Trials for MDMA-PTSD Drug-Disease Pair

Database(s): CENTRAL database of trials

Search date: July 19, 2022

#	Search String	Results	Annotations
#1	MeSH descriptor: [3,4-Methylenedioxyamphetamine] this term only	27	
#2	MeSH descriptor: [N-Methyl-3,4-methylenedioxyamphetamine] this term only	211	
#3	((MDMA OR methylenedioxymethamphetamine OR methylene-dioxymethamphetamine OR methylene-dioxy-methamphetamine OR midomafetamine)):ti,ab,kw	395	
#4	#1 OR #2 OR #3	411	
#5	MeSH descriptor: [Stress Disorders, Traumatic] explode all trees	3260	
#6	((trauma* OR posttrauma* OR PTSD)):ti,ab,kw (Word variations have been searched)	30414	
#7	(((stress NEXT/2 (syndrome or disorder)) OR PTSS)):ti,ab,kw	5712	
#8	#5 OR #6 OR #7	30606	
#9	#4 AND #8	60	Searched in "Trials" only Restricted to publication year 2010 to present

Table A2. PsycINFO Search for Experimental Trials for MDMA-PTSD Drug Disease Pair

Database(s): Advanced search in APA PsycInfo via EBSCOhost Research Databases

Search date: July 19, 2022

#	Search String	Results	Annotations
S1	DE “Experimental design” OR DE “Quasi Experimental Methods”	12,620	
S2	DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials" OR DE "Clinical Trials"	13,295	
S3	DE "Random Sampling"	929	
S4	DE "Pretesting" OR DE "Posttesting"	805	
S5	TI (randomised OR randomized) OR AB random* OR TI trial	239,858	
S6	DE "sample size" AND AB (assigned OR allocated OR control)	487	
S7	DE "placebo"	6,295	
S8	AB (control W5 group)	106,066	
S9	AB (cluster W3 RCT)	191	
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	333,513	Adapted RCT filter from Glanville et al 2019[39]
S11	((DE "Posttraumatic Stress Disorder" OR DE "Complex PTSD" OR DE "DESNOS") OR (DE "Posttraumatic Stress")) OR TI ((trauma* OR postrauma* OR PTSD)) OR AB ((trauma* OR postrauma* OR PTSD)) OR TI ((stress N2 (syndrome OR disorder)) OR (PTSS)) OR AB ((stress N2 (syndrome OR disorder)) OR (PTSS))	143,797	PTSD line – controlled vocabulary and free text
S12	DE "Methylenedioxymethamphetamine" OR TI ((MDMA OR methylenedioxymethamphetamine OR midomafetamine)) OR AB ((MDMA OR methylenedioxymethamphetamine OR midomafetamine))	2,735	MDMA line – controlled vocabulary and free text
S13	S10 AND S11 AND S12 • Limited to publication year 2010 to 2022	37	

APPENDIX B – RISK OF BIAS DATA EXTRACTION KEY AND DETAILED BIAS ASSESSMENT[36,42]

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
ClinicalTrials.gov NCT ID		The unique ID identifying this study registered at ClinicalTrials.gov, for all studies performed in whole or in part in the US.	NCT03537014
Publications, Manuscripts, and Reports		Subject to the narrative documents summarizing the study. May include detailed protocols, RCTs published in peer-reviewed journals, and/or non-published manuscripts.	Mitchell et al. 2021; MAPS Public Benefit Corporation MAPP1 Protocol IND #063384.
ROB Assessment for the Domain-based and Jadad Approach			
Randomization			
Random sequence generation methods		Assessed at the NCT ID level, the methods used for allocation sequence generation.	Random-numbers table; random-sequence-generating software; central methods center randomization. (Coin-flipping and die-throwing not recommended.)[38]
	Domain-based assessment	High risk: The study is not described as randomized, or the method of allocation sequence generation is not truly random. Unclear risk: No random allocation sequence method is adequately described. Low risk: An adequate method for generating random allocation sequences is described.	n/a

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
	Jadad assessment	2 points: The study is described as randomized, and an adequate method of generating random allocation sequences is described. 1 point: The study is described as randomized, but an appropriate method is not described. Otherwise, 0 points.	n/a
Allocation concealment methods		Assessed at the NCT ID level, the methods used to conceal allocation sequence generation from recruiting personnel.	Employing an independent third party to perform randomization.
	Domain-based assessment	High risk: The study is described as open-label, or it is otherwise clear that recruiting investigators had advance knowledge of treatment assignments. Unclear risk: No method for concealing allocation sequences from recruiting investigators is described. Low risk: The study describes an adequate method for concealing allocation sequences from recruiting personnel.	n/a
Blinding/Masking of Participants and Personnel			
Participant blinding/masking methods		Assessed at the NCT ID level, the methods used to blind participants to their allocation sequence and treatment arm assignment.	Masking: identical agents provided in unlabeled containers; blinding: lack of awareness of the allocated treatment
Evidence of participant unblinding/unmasking		Describe any information that suggests that participants may have been aware of their treatment status.	When asked, the majority of participants were able to correctly guess their treatment arm.

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
	Domain-based assessment	High risk: The study is described as open-label or there is evidence that participants were able to accurately guess their treatment assignment. Unclear risk: Due to the nature of the intervention, there is a theoretical risk that participants could accurately guess their treatment assignment. Low risk: Neither of the above applies, and participant blinding was described after unblinding as having been successful.	n/a
Clinician blinding/masking methods		Assessed at the NCT ID level, the methods used to blind those performing the intervention to the treatment assignment.	Masking: identical agents provided in unlabeled containers; blinding: lack of awareness of the allocated treatment
Evidence of clinician unblinding/unmasking		Describe any information that suggests that clinicians may have been aware of participant treatment status.	When asked, clinicians were able to correctly guess the majority of participants' treatment arm.
	Domain-based assessment	High risk: The study is described as open-label or there is evidence that clinicians were able to accurately guess participant treatment assignment. Unclear risk: Due to the nature of the intervention, there is a theoretical risk that clinicians could have unmasked the participant's treatment assignment. Low risk: Neither of the above applies, and clinician blinding was described after unblinding as having been successful.	n/a

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
	Jadad assessment	2 points: (A) The study is described as at least "double blind" and (B) the control treatment (eg, placebo) is described as indistinguishable. 1 point: Either condition (A) or (B) above is met, but not both. Otherwise, 0 points.	n/a
Blinding/Masking of Outcome Assessors			
Outcomes assessor blinding/masking methods		Assessed at the outcome level, the methods that were used to blind those determining outcomes of the interventions in treatment arms.	Assessors are independent and third-party and only assess anonymous CAPS data.
Evidence of outcomes assessor unblinding/ unmasking		Describe any information that suggests that those determining outcomes may have been aware of participant treatment assignment.	Outcomes assessors had access to vital sign data (eg, pulse, blood pressure) of treatment sessions.
	Domain-based assessment	High risk: The study is described as open-label or there is evidence that outcomes assessors were able to accurately guess participant treatment assignment. Unclear risk: Due to the nature of the intervention, there is a theoretical risk that outcomes assessors could have unmasked the participant's treatment assignment. Low risk: Neither of the above applies, and outcomes assessor blinding was described after unblinding as having been successful.	n/a
Analytic Subset and Outcomes			
Analytic subset		Which analytic subsets were analyzed in this report for this outcome?	ITT (includes all randomized participants) mITT (modified ITT), PP (per protocol; analyzing outcomes for a defined subset of the total randomized population.

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
Attrition		Describe the attrition for the analytic subsets specified.	2 of 20 in experimental group (10%; withdrew due to AE; 1 of 18 in comparator group (5.6%; withdrew due to lost to follow-up)
	Domain-based assessment	High risk: Any overall attrition above 5% or any between-group differences in attrition Unclear risk: Any attrition in which reasons were not described. Low risk: No attrition or low and non-differential attrition that is adequately described.	n/a
	Jadad assessment	1 point: attrition is given if attrition is described for each group including numbers excluded along with reasons. Otherwise, 0 points.	n/a
		Jadad Score	
Jadad Total Score		Sum of individual Jadad scale points: Up to 2 points for randomization, up to 2 points for blinding/masking, up to 1 point for attrition.	2 + 2 + 1 = 5
		Outcome Reporting Bias	
Number of randomized participants		For studies with more than 1 source (eg, clinical trial registry, publication), describe any discrepancies in numbers of eligible participants, numbers of randomized participants to treatment groups, or numbers being lost to follow-up.	Clinical trial data reporting 16 eligible and 15 randomized; publication's attrition figure reporting 15 eligible and 15 randomized.
Number with events		For studies with more than 1 source (eg, clinical trial registry, publication), describe any discrepancies in numbers of participants with efficacy or safety outcomes in either treatment group.	Clinical trial data reporting 15 randomized and 15 analyzed, versus publication reporting 15 randomized and 13 analyzed.

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
Outcomes assessed and reported		For studies with more than 1 source (eg, clinical trial registry, publication, including protocol), describe whether there are any discrepancies between reports about which outcomes were to be assessed.	Protocol indicates the collection of secondary outcomes: participant-reported PTSD symptoms using the PDS, GAF, and PTGI, but these are not reported by either ClinicalTrials.gov or the publication.
	Assessment	High risk: Any of the following: (A) discrepancies between reports in numbers of eligible participants, randomized participants, participants lost to follow-up, or participants with events, or clear discrepancies, or (B) overt contradictions between reports about which outcomes were assessed/evaluated. Unclear risk: Possible but not overt discrepancies between reports, or a lack of a published protocol. Low risk: No evidence of discrepancies between reports.	n/a
Supplemental ROB Assessment			
Adherence and Re-training of Therapists			
Adherence to MDMA and psychotherapy		Report any information from any source (eg, clinical trial registry, publication) about adherence/compliance to the study regimen (ie, drug/comparator + therapy).	The number/proportion of participants completing all therapy sessions; reference to the psychotherapy protocol.
Re-training of therapists		Report any information from any source (eg, clinical trial registry, publication) about training of the therapists, re-training, and/or fidelity to the psychotherapeutic approach.	Verification by adherence raters to the standardized therapeutic approach; reference to the psychotherapy protocol.
	Assessment	Summarize information about adherence and re-training.	n/a

Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

Table B1. Risk of bias (ROB) Data Extraction Key Organized by Bias Element

Bias Component	Assessment	Criteria and/or Description	Example(s)
Funding Bias			
Study sponsorship		Report the sponsor (ie, organization providing financial support) of the study.	Multidisciplinary Association for Psychedelic Studies (MAPS)
Role of sponsor		Report the sponsor's role, if anything, in the design, conduct or reporting of the study.	First and last author are employees of the sponsor. Sponsor was not involved in outcomes assessment.
	Assessment	Summarize information about funding bias.	n/a

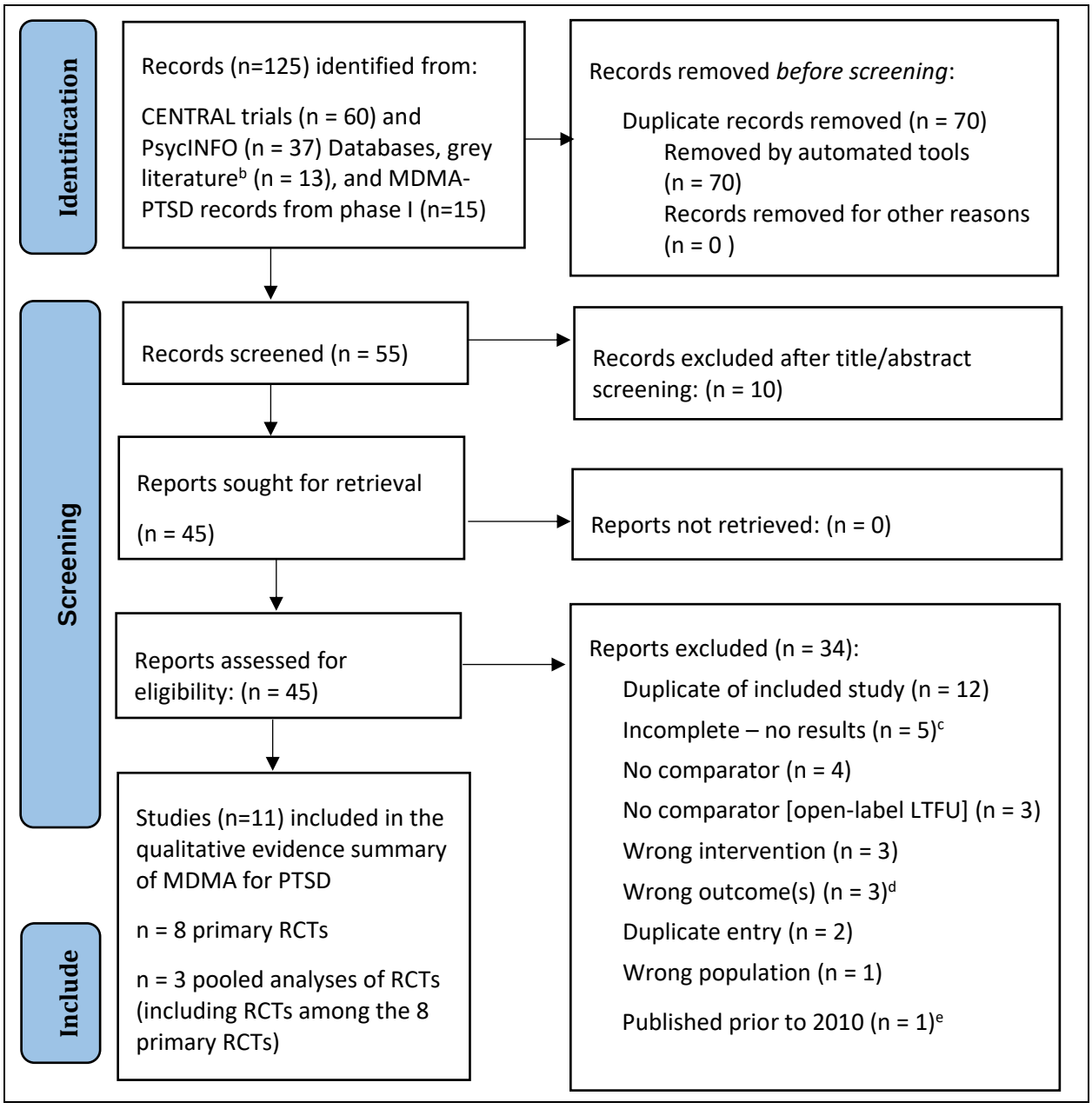
Abbreviations: CAPS, Clinician-administered PTSD Scale; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; MAPS, Multidisciplinary Association for Psychedelic Studies; MDMA, 3,4-Methylenedioxymethamphetamine; n/a, not applicable; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias.

Blinding vs masking: This ROB analysis uses "blinding" to refer to concealment of the knowledge of treatment arm assignments from subjects and study personnel (ie, blinding of persons), and "masking" to refer to rendering the treatment agents indistinguishable from each other (ie, masking of agents). Included studies may use these two terms differently.

APPENDIX C – SCREENING OF STUDIES

Phase I of the evidence review included a search of Ovid-Medline and Embase for experimental trials for multiple medications (MDMA being 1 of 5) and conditions. Details of this search are reported in the prior report. In brief, the phase I search retrieved 933 records, and 43 of these were included in the phase I annotated bibliography (including 5 unique trials and 4 pooled analyses of MDMA for PTSD). The diagram below shows the flow from identification and screening to inclusion of studies.

Figure C1. PRISMA Diagram[a]: Identification and Inclusion of Studies for Evidence Review



Abbreviations: LTFU, long-term follow-up; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder ; RCT, randomized controlled trial

[a] Modified from Page et al. 2021[79]

[b] Identified from trials in the 14th Edition (March 2022) of the Multidisciplinary Association for Psychedelic Studies (MAPS) Investigator's Brochure

[c] Registered but incomplete trials include NCT04077437 (a second phase 3 trial of MDMA-assisted therapy among people with moderate PTSD severity),[61] ACTRN12612000219886 (withdrawn trial),[80] NCT03752918,[81] NTR6670,[82] and NCT04784143 (phase 2 open-label trial comparing 2 versus 3 MDMA-assisted therapy sessions).[50]

[d] A few publications report exploratory, non-PTSD outcomes from included MDMA-assisted therapy trials. Examples of primary outcomes among these studies are eating disorder symptoms,[83] alcohol or drug use disorder symptoms,[78] and frequency of empathic or ensuic utterances during MDMA-assisted therapy.[84]

[e] One trial appearing to otherwise meet our criteria was published prior to 2010. This was a very small (n=6) trial of women with chronic, treatment-resistant PTSD with a history of sexual assault trauma. They administered escalating MDMA doses (50 mg [n= 3 participants]; 75 mg [n=5 participants) or placebo [n=6 participants]. All participants completed 6 non-drug psychotherapy sessions. Improvements in PTSD symptoms were associated with MDMA; however, a smaller than planned number of participants was enrolled due to political pressure at the site, and thus the study was underpowered to assess the outcomes.[85]

APPENDIX D – TRIAL STUDY DESIGN SUPPLEMENTARY INFORMATION

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
Mitchell 2021[32,60] NCT03537014 Phase 3, multicenter (US, Canada, Israel), randomized (1:1), participant/staff/sponsor blinded/outcome-rater blinded, parallel group, inert placebo-controlled trial Duration including treatment period and follow-up: ~27 weeks	Adults (mean age 41 years; 65% female) with PTSD per the PCL-5 (DSM-5-based PTSD checklist) with baseline CAPS-5 total score ≥ 35 *PTSD duration:* ≥ 6 months before screening	• *Psychiatric diagnoses*: primary psychotic disorder, BPD I, dissociative identity disorder, MDD with psychotic features, personality disorders, active alcohol or substance use disorder • *Cardiac diagnoses*: arrythmia disorders, baseline QT/QTc interval prolongation, uncontrolled hypertension, other conditions where sympathomimetic drug could be harmful • *Other:* pregnancy/lactation, weight ≤ 48 kg, patients unwilling to comply with lifestyle changes (eg, d/c current psychiatric meds)	• Dose (total 80-180 mg MDMA per session; total cumulative dose: 240-480 mg) given during three 8h psychotherapy sessions separated by ~4 weeks • *Session 1:* MDMA 80 mg + 40 mg 1.5-2.5h later (optional) • *Session 2 and Session 3:* MDMA 120 mg + 60 mg 1.5-2.5h later (optional) (MDMA arm: 1 patient chose not to take the supplemental dose; and 2 patients chose to not escalate to the 120 mg dose, remaining at the 80 mg dosage)	Inert placebo matched to MDMA and delivered to match the MDMA arm	Non-directive manualized therapy *Total sessions:* 15 *(including ~18h non-drug sessions; and ~24h drug sessions)* • Preparatory: Three, 1.5h sessions over 6 weeks • Experimental: Three, 8h sessions spaced by 3-5 weeks • Integration: Three, 1.5h sessions following each experimental session (9 total); first session the morning after the experimental session, and the following sessions over 3-4 weeks, spaced by ~1 week. Additional sessions allowed by request (14 participants, 10 in MDMA arm completed these)
Unpublished [44,59] NCT01958593	Adults (mean age 48 years, 50% female) with severe PTSD	• No psychiatric or medical conditions considered risky	• Dose (total 125-187.5 mg MDMA per session; total cumulative dose:	Inert placebo matched to MDMA and	Non-directive manualized therapy

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
Terminated early Phase 2 pilot, single site (Canada), randomized (7:5), triple-masked (participant/investigator/ outcome-rater), parallel group, inert placebo-controlled trial Duration including treatment period and follow-up: 15-18 months The blinded period was followed by an open-label period (known as "Stage 2") with 1 additional MDMA dose (for active MDMA arm) or cross-over to MDMA for comparator[b]	(CAPS-4 score ≥ 60[c]) and failure or intolerance to at least 1 other PTSD treatment *PTSD duration:* ≥ 6 months before screening	• No active abuse of illegal drugs • *Other:* pregnancy/lactation, weight ≤ 48 kg, patients unwilling to comply with lifestyle changes (eg, d/c current psychiatric meds)	240-375 mg MDMA) given during two 8h sessions separated by 2-5 weeks • *Session 1 and session 2:* MDMA 125 mg + 62.5 mg 1.5-2.5h later (optional)	delivered to match the MDMA arm	*Total sessions: ~11 (including ~13.5h non-drug sessions; and 16h drug sessions)* • Preparatory: Three, 1.5h sessions completed within 5-8 weeks of enrollment • Experimental: Two, 8h sessions spaced by 2-5 weeks • Integration: Three, 1-1.5h sessions following each experimental session (6 total); first session the morning after the experimental session (1-1.5h), and the following sessions (1.5h) prior the next experimental session. Additional integrative sessions (including by telemedicine or phone) allowed if needed.
Unpublished [45] NCT01689740 *Completed* Phase 2 pilot, single site (Israel), randomized (3 active MDMA: 5 low-dose MDMA), triple-masked (participant/investigator/	Adults (between ages 18-65, 40% female) with moderate-severe PTSD (per CAPS) and failure or intolerance to at least 1 other PTSD treatment.	• Presence of psychiatric or medical conditions considered risky • Active abuse of illegal drugs • *Other:* pregnancy/lactation, weight ≤ 48 kg, patients unwilling to comply with	• Dose (MDMA 187.5 mg per session) given during two 6-8h sessions separated by 3-5 weeks • *Session 1 and session 2:* MDMA 125 mg +	Matched active placebo (MDMA 25 mg + optional 12.5 mg) delivered to match the active MDMA arms	Non-directive manualized therapy *Total sessions: ~11 (unclear total non-drug duration; drug duration 12-16 h)* • Preparatory: Three sessions of unknown duration spaced by ~1 week

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
outcome-rater) and partially open-label*, parallel group, active placebo-controlled trial *2/5 participants receiving active MDMA received it open-label. This open-label period was used to standardize therapy delivery. Duration including treatment period and follow-up: 14-18 months The blinded period was followed by an open-label period (known as "Stage 2") with cross-over to active MDMA for the comparator[b]	*PTSD duration:* ≥ 6 months before screening	lifestyle changes (eg, d/c current psychiatric meds)	62.5 mg 1.5-2.5h later (optional)		• Experimental: Two, 6-8h sessions spaced by 3-5 weeks • Integration: Three, 1-1.5h sessions following each experimental session (6 total); first session (1.5h) the morning after the experimental session with daily phone contact during the following week, and the following sessions (1-1.5h) spaced by ~1 week. Additional sessions allowed if considered necessary.
Ot'alora 2018[46,52,58] NCT01793610 Phase 2 pilot, randomized (2 MDMA 125: 1.5 MDMA 100 mg: 1 MDMA 40 mg),	Adults (mean age 42 years, 68% female) with moderate-severe (baseline CAPS-4 score ≥ 50) chronic PTSD and failure or intolerance	• *Psychiatric diagnoses*: primary psychotic disorder, BPD I, dissociative identity disorder, personality disorders, active alcohol or substance use disorder, serious suicide risk, eating	• Dose (total 100 or 125 mg - 150 mg to 187.5 MDMA per session; total cumulative dose: 200-375 mg MDMA) given during two 8h	Matched active placebo (MDMA 40 mg + optional 20 mg) delivered to match the	Non-directive manualized therapy *Total sessions: ~11 (including ~13.5h non-drug sessions; and 16h drug sessions)*

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
single-site (US), triple-masked (participant/investigator/ outcome-rater, parallel group, active-placebo controlled, dose-finding trial Duration including treatment period and follow-up: 15-18 months The blinded period was followed by an open-label period (known as "Stage 2") with 1 additional MDMA dose (for MDMA 100-125 arm) or cross-over to MDMA for comparator[b]	to at least 1 other PTSD treatment *PTSD duration:* ≥ 6 months before screening	disorder with current purging • *Cardiac diagnoses*: uncontrolled hypertension, atherosclerosis, significant cardiovascular or cerebrovascular disease, other conditions where sympathomimetic drug could be harmful • *Other:* pregnancy/lactation, weight < 48 kg, patients unwilling or not able to comply with lifestyle changes (eg, d/c current psychiatric meds), history of hyponatremia or hyperthermia, consistent or recent prior MDMA use, diabetes type 1 or 2, history or current liver disease, other significant medical conditions	sessions separated by 3-5 weeks • *Session 1 and session 2:* MDMA 100 mg or 125 mg (2 separate study arms) + ½ the original dose (50-62.5 mg) 1.5-2.5 h later (optional)	active MDMA arms	• Preparatory: Three, 1.5h sessions spaced by ~1 week • Experimental: Two, 8h sessions spaced by 3-5 weeks • Integration: Three, 1-1.5h sessions following each experimental session (6 total); first session (1-1.5h) the morning after the experimental session with daily phone contact during the following week, and the following sessions (1.5h) spaced by ~1 week. Additional sessions allowed if considered necessary.
Mithoefer 2018 [47,53,57] NCT01211405 Phase 2 pilot, randomized (2 MDMA 125: 1 MDMA 75 mg: 1 MDMA 30 mg),	Adults (mean age 37 years, 27% female) with moderate-severe (baseline CAPS-4 score ≥ 50) chronic PTSD from a	• All major medications with a few exceptions (eg, controlled hypertension or treated hypothyroidism) • *Psychiatric diagnoses:* many except for a few (anxiety	• Dose (total MDMA per session, 125-187.5 mg [full dose] or 75-112.5 mg [medium dose]) given during two 6-8h	Matched active placebo (MDMA 30 mg + optional 15 mg) delivered to match the	Non-directive manualized therapy *Total sessions: ~11 (including ~13.5h non-drug sessions; and 16h drug sessions)*

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
single-site (US), triple-masked (participant/investigator/ outcome-rater), parallel group, active-placebo controlled, dose-response trial Trial not powered to detect differences Duration including treatment period and follow-up: 18-24 months The blinded period was followed by an open-label period (known as "Stage 2") with 1 additional MDMA dose (for MDMA 125 arm) or cross-over to MDMA (100-125 mg) for the comparators (ie, MDMA 75 mg or 30 mg)[b]	service-related trauma and failure or intolerance to at least 1 other PTSD treatment *PTSD duration:* ≥ 6 months before screening	disorders, non-bipolar I affective disorders, eating disorders without purging, substance use disorders in remission) • *Other:* pregnancy or lactation, weight < 48 kg, other conditions considered risky for MDMA use, participants unable to taper off prohibited medications (including current PTSD treatments)	sessions separated by 3-5 weeks • *Session 1 and session 2:* MDMA 75 mg or 125 mg (2 separate study arms) + ½ the original dose (37.5-62.5 mg) 1.5-2h later (optional)	active MDMA arms	• Preparatory: 3, 1.5h sessions spaced by ~1 week • Experimental: 2, 6-8h sessions spaced by 3-5 weeks • Integration: 3, 1.5h sessions following each experimental session (6 total); first session the morning after the experimental session with daily phone contact during the following week, and the following sessions prior the next experimental session, or within 4 weeks of the last experimental session. Additional sessions allowed if considered necessary.
Oehen 2013[48,54] NCT00353938	Adults (mean age 41 years, 83% female) with chronic, treatment-resistant PTSD (baseline	• *Psychiatric diagnoses*: primary psychotic disorder, BPD I, borderline personality disorder, dissociative identity	• Dose (total MDMA per session, 125-187.5 mg [active dose] given	Matched active placebo (MDMA 25 mg + optional 12.5 mg) delivered	Non-directive manualized therapy *Total sessions: 15?** (12 non-drug sessions and 3 drug sessions)* • Preparatory: 2 sessions

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
Phase 2 pilot, randomized (2 active MDMA:1 comparator), multi-site (primarily Switzerland, also France), triple-masked (participant/investigator/ outcome-rater), parallel group, active-placebo controlled, trial Trial not powered to detect differences Duration including treatment period and follow-up: unknown; 12 months after the treatment period planned The blinded period was followed by an open-label period (known as "Stage 2" and "Stage 3") with 3 additional MDMA doses and 7 therapy sessions (for active MDMA arm) or cross-over to active MDMA for the comparators[b]	CAPS-4 score ≥ 50) with prior psychotherapy treatment (for at least 6 months) and prior drug therapy (SSRI for at least 3 months))	disorder, active alcohol or substance use disorder, eating disorder with current purging • *Cardiac diagnoses*: uncontrolled hypertension, peripheral vascular disease, other significant cardiovascular or cerebrovascular history • *Other:* pregnancy/lactation, weight <50 kg, significant prior history of MDMA use, history of hyponatremia or hyperthermia, most other significant medical history including neurologic disorders such as seizures, patients unwilling to comply with lifestyle changes (eg, d/c current psychiatric meds)	during three 8h sessions • *Session 1-3:* MDMA 125 mg + 62.5 mg 2.5h later (optional)	to match the active MDMA arms	• Experimental: 3, 8h sessions • Integration: 3 sessions (inferred as 9 total); first session the morning after the experimental session and the following 2 sessions prior the next experimental session. **The published report states there were 12 non-drug psychotherapy sessions, though this does not match the number of preparatory an integratory sessions reported in other sections of the text.
Mithoefer 2011[49,55]	Adults ages 21-70 years (mean 40.4	• *Psychiatric diagnoses:* borderline personality	• Dose (total MDMA per session, 125-187.5 mg	Inert placebo matched to	Non-directive manualized therapy

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
NCT00090064 Phase 2 pilot, randomized (6 active MDMA:1 placebo), multi-site (US), triple-masked (participant/investigator/ outcome-rater), parallel group, placebo controlled, trial Duration including treatment period and follow-up: unknown; at least 10 months follow-up after completion of the study planned The blinded period was followed by an open-label period (known as "Stage 2") consisting of 1 an additional MDMA session for the active MDMA arm, and crossover to 3 experimental sessions for the placebo comparator arm[b]	years; 85% female) Adults (mean age 41 years, 83% female) with chronic (≥ 5 years), moderate-severe PTSD (CAPS score ≥ 50) resulting from military- or crime-related trauma with failure or intolerance to at least 1 prior treatment (drug therapy for ≥ 3 months or psychotherapy for ≥ 6 months)	disorder, BPD I, other axis I psychiatric conditions (EXCEPT for anxiety disorders, non-BPD-1 affective disorders, substance use in remission, eating disorders *without* active purging) • Active abuse of illegal drugs • *Other:* pregnancy/lactation, weight <50 kg, patients unwilling to comply with lifestyle changes (eg, d/c current psychiatric meds), presence of psychiatric or medical conditions considered risky	[active dose]) given during two 8-10h sessions about 3-5 weeks apart • *Session 1 and 2:* MDMA 125 mg + 62.5 mg 2-2.5h later (optional)	MDMA and delivered to match the MDMA arm	*Total sessions: ~12 (including ~15h non-drug sessions; and 16h drug sessions)* • Preparatory: 2, 1.5h sessions spaced by within 6 weeks • Experimental: 2, 6-8h sessions spaced by 3-5 weeks • Integration: 4, 1.5h sessions following each experimental session (8 total); first session the morning after the experimental session with daily phone contact during the following week, and the following 3 sessions within the month after each experimental session. Additional sessions allowed if considered necessary.

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]
Unpublished[43] NCT00402298 *Terminated early* Phase 2, randomized single-site (Israel), triple-masked (participant/investigator/ outcome-rater), parallel group, active-placebo controlled, trial Duration including treatment period and follow-up: unknown; 12 months after the treatment period planned The blinded period was followed by an open-label period with cross-over to active MDMA for the comparators[b]	Adults (primarily ages 18-65 years, 0% female) with PTSD due to war or terrorism trauma that persists despite at least 1 other treatment (drug or psychotherapy) Participants were Hebrew-speaking and were allowed to continue seeing an outside therapist during the trial as long as the frequency of visits was the same as prior to the trial.	• *Psychiatric diagnoses*: psychotic disorder, BPD I, borderline personality disorder, dissociative identity disorder, active alcohol or substance use disorder, eating disorder with current purging, high suicide risk • *Cardiac diagnoses*: uncontrolled hypertension, peripheral vascular disease, other significant cardiovascular or cerebrovascular history • *Other*: pregnancy, weight <50 kg or >105 kg, significant prior history of MDMA use, history of hyponatremia or hyperthermia, most other significant medical history other than treated hypothyroidism including neurologic disorders such as seizures, patients unwilling to comply with lifestyle changes (eg, d/c current psychiatric meds)	• Dose (total MDMA per session, 125-187.5 mg [active dose] given during 2 6-8h sessions 3-5 weeks apart • *Session 1 and 2:* MDMA 125 mg + 62.5 mg 2-2.5h later	Matched active placebo (MDMA 25 mg + 12.5 mg) delivered to match the active MDMA arms	Non-directive manualized therapy *Total sessions: 8-10 (~6-11 h non-drug sessions and 12-16h drug sessions)* • Preparatory: Two 1h sessions • Experimental: Two, 6-8h sessions separated by 3-5 weeks • Integration: 2-3 sessions (1-2h) following each experimental session (4-6 total); first session (1-1.5h) 24h after the experimental session and the following 1-2 sessions (1-2h) weekly prior to the experimental session.

Table D1. Overview of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) NCT Design	PTSD Population	Selected Exclusion Criteria	Active MDMA Regimen(s)[a]	Comparator Regimen[a]	Psychotherapy Regimen[a]

Abbreviations: BPD, bipolar disorder type I; d/c, discontinued; h, hour; kg, kilogram; MAPS, multidisciplinary association for psychedelic studies; MDD, major depressive disorder; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; QT, the cardiac QT interval; QTc, cardiac QT interval corrected for heart rate;

[a] Participant sessions with co-therapists. During dosing/experimental sessions, active MDMA or the comparator is given to participants. The psychotherapy regimen was delivered to all treatment groups. **Description is based on the blinded trial period.**

[b] This focus of information in this table is the blinded study period (ie, any MDMA doses and psychotherapy during the open-label follow-up period are not described)

[c] The NCT0195893 study protocol lists a CAPS-4 criteria of 60 (corresponding to severe symptoms), but in another place, describes the target population as being people with moderate-severe PTSD symptoms. The summary study by Mithoefer 2019 also lists a CAPS-4 score ≥ 60 as a criteria for this study.[33]

Table D2. Overview of Sponsor-conducted Summary Studies[a] of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) Included NCTs	Study Design	PTSD Population	Treatment Groups[a] (n included in analysis)	Number of Drug-assisted Therapy Sessions	Primary Endpoint Measurement[b]
Ponte 2021[65] NCT01958593; NCT0121140; NCT01689740; NCT01793610	Summary of 4 phase 2 RCTs that collected the PSQI outcome	Adults (mean ~40y/46% female) with moderate-severe chronic PTSD • Mean BL CAPS-4 TS (SD) = active MDMA: 90 (18); comparator 86 (10) • Mean PTSD duration (SD) = Active MDMA: 21 y (19); comparator: 13 y (11) • Variable trauma history (71.4% combat-related) • Prior MDMA exposure: active MDMA: 32%; comparator: 19%	Active MDMA 75-125 mg: (n = 46) **Vs** Comparator 0-40 mg MDMA: (n = 16)	2	4-8 wks
Gorman 2020[86] NCT01793610; NCT01958593; NCT01211405	Summary of 3 phase 2 RCTs that collected the PTGI outcome	Adults (mean ~40y/48% female) with moderate-severe chronic PTSD • Mean BL CAPS-4 TS (SD) = active MDMA: 90 (18); comparator: 88 (11) • Mean PTSD duration (SD) = active MDMA: 20 y (19); comparator: 12 y (12) • Variable trauma history (35% war-related) • Prior MDMA exposure: active MDMA: 36%; Comparator: 20%	Active MDMA 75-125 mg: (n = 45) **Vs** Comparator 0-40 mg MDMA: (n = 15)	2	4 wks
Mithoefer 2019[33] NCT00090064; NCT00353938; NCT0195893; NCT01211405; NCT01689740; NCT01793610	Summary of 6 phase 2 RCTs	Adults (mean ~41y/58.1% female) with moderate-severe chronic PTSD that failed ≥ 1 prior therapy • Mean BL CAPS-4 TS (SD) = 85 (18) • Mean PTSD duration (SD) = 18 y (16) • Variable trauma history • 2% of participants without any prior therapy • 30% with prior MDMA exposure (active MDMA: 32%; comparator: 23%)	Active MDMA 75-125 mg: (n = 72) **Vs** Comparator 0-40 mg MDMA: (n = 31)	2[c]	3-8 wks

Abbreviations: MAPS, multidisciplinary association for psychedelic studies; MDMA, 3,4-methylenedioxymethamphetamine; mg, milligrams; PTGI, posttraumatic growth inventory; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial; SD, standard deviation; wks, weeks; y, years;

Table D2. Overview of Sponsor-conducted Summary Studies[a] of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD, 2010-present

Study (first author, publication year) Included NCTs	Study Design	PTSD Population	Treatment Groups[a] (n included in analysis)	Number of Drug-assisted Therapy Sessions	Primary Endpoint Measurement[b]

[a] Each drug given in combination with manualized therapy. Treatment groups are based on the drug administered during each experimental therapy session. The MDMA dosage range reported here are for the initial dose given during MDMA-assisted sessions. Doses of MDMA or control were given as an initial dose at the start of the experimental therapy session, and if tolerated, an optional second dose (at half the dosage of the original dose) was given approximately 1.5-2.5 h later.

[b] After last experimental drug-assisted session.

[c] The primary outcome of the summary study is based on 2 drug-assisted sessions; however, 1 of the included trials studied 3 blinded dosing sessions

APPENDIX E – KEY COMPONENTS OF MAPS MDMA-ASSISTED PSYCHOTHERAPY

List of MDMA-assisted therapy elements according to the MAPS protocol version 8.1 (pages 7-8)[56‡‡‡]:

1. Ensure participant wellbeing
2. Therapist should be appropriately qualified and trained
3. Prepare the participant
4. Stage the setting – "…appropriate set, setting, and support system during the MDMA-assisted sessions and follow-up sessions…"[56]
5. Must establish therapeutic alliance and trust with participant
6. "A **nondirective approach to therapy** based on **empathetic rapport and empathetic presence** should be used to support the participant's own unfolding experience and the body's own healing process. A non-directive approach emphasizes invitation rather than direction."[56]
    a. "…the locus of movement or therapeutic action is coming from within the participant rather than the therapists."[56]
7. Encourage the participant's self-directed healing
8. "**Intervention** in the form of guidance or redirection, when deemed appropriate, can be used to facilitate the participant's processing. Therapists must attend to balancing their responsibilities as facilitators as a noninvasive empathic witnesses."[56]
9. "The therapy should enable the **processing of trauma** rather than the avoidance of traumatic memories; however, this should be done with respect for protective mechanisms, which are referred to in different models of therapy as 'resistance', 'defenses', 'protectors', etc. The therapists should facilitate awareness of and curiosity about any apparent resistance that arises rather than simply attempting to overcome it."[56]
10. "Therapists seek to **maximize the benefits of the inner experience catalyzed by MDMA,** while at the same time **ensuring that the participant is safe and is not re-traumatized** by internal conflicts that may arise**."[56]**
11. **"**Therapeutic techniques should be available to **address somatic manifestations of trauma** that arise. These may include one or more approaches such as nurturing touch, focused bodywork, breathing techniques, or other approaches to somatosensory processing."[56]
12. **"**It is important to include various tools such as music, focused bodywork, breathing, or other techniques in the therapeutic setting to **evoke and support emotional experience** while avoiding distraction from the participant's experience."[56]
13. **"Integration** is viewed as an **essential and ongoing process** as the inner experiences catalyzed by MDMA-assisted sessions continue to unfold. Follow-up contact with the therapists by phone and during scheduled integration visits is necessary to support successful integration. During these visits the therapists aim to address any difficulties that may have arisen following MDMA-assisted sessions and to anchor the lessons gained in a non-ordinary state of consciousness so they can be integrated into daily life."[56]

‡‡‡ Version 8.1 protocol was published in August 2017; this version was likely used in the completed phase 3 trial.

14. **“**The therapy requires **a thorough understanding of the nature of MDMA effects** and the **non-linear manner** in which they can lead to healing.”[56]

APPENDIX F – EFFICACY ANALYSES BY INCLUDED SUMMARY STUDIES

Table F1. Efficacy of Sponsor-Conducted Summary Studies[a] of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study First Author & Publication Year NCT *Comparison (n)[b]*	CAPS Outcome		Dichotomous Response Outcomes	
	CAPS Measure and Timepoint[b]	**Mean Change in CAPS per Arm (SEM or SD)** (Between Group Difference [BGD] and P-value vs Control Group, if provided)	**Response Measures**	**Proportion of Patients with Response (%)**
Mithoefer 2019[33] NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610 *Active MDMA 75-125 mg (n=74) for 2 sessions vs Control (MDMA 0-40 mg, n=31)*	CAPS-4 total severity score at 3 weeks to 2 months post 2nd experimental session in the modified ITT	Active MDMA, n=72: –32.43 (SEM 3.20) Comparator, n=31: –10.47 (SEM 4.46)	Loss of PTSD diagnosis	Active MDMA: 39/72 (54.2%) Comparator: 7/31 (22.6%)
Ponte 2021[65d] NCT01958593, NCT01211405, NCT01689740, NCT01793610 *Active MDMA 75-125 mg (n=50) for 2 sessions vs Control (MDMA 0-40 mg, n=18)*	Change in CAPS-4 total severity score at 1 to 2 months post 2nd treatment session in patient set completing at least one blinded session and one follow-up assessment	Active MDMA, n = 46: –33.98 (SD 26.46) Comparator, n=16: –12.38 (SD 16.38)	NR	
Gorman 2020[86d] NCT01211405, NCT01793610, NCT01958593 *Active MDMA 75-125 mg (n=45) for 2 sessions vs Comparator (MDMA 0-40 mg, n=15)*	Change in CAPS-4 total severity score at 1 month post 2nd treatment session in patient set completing at least one blinded session and one follow-up assessment	MDMA, n=44: –35.1 (27.45) Comparator, n=15: –12.8 (15.88)	Loss of PTSD diagnosis	Active MDMA: 23/44 (52.3%) Comparator: 5/15 (33.3%)

Abbreviations: APBO, active placebo as low-dose MDMA; BGD, between group difference; CAPS-5, Clinician-administered PTSD for DSM-5; CAPS-4, Clinician-administered PTSD for DSM-4; CI, confidence interval; *d*, between-group treatment effect size using Cohen's d; DSM, Diagnostic and Statistical

Table F1. Efficacy of Sponsor-Conducted Summary Studies[a] of Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study First Author & Publication Year NCT *Comparison (n)[b]*	CAPS Outcome		Dichotomous Response Outcomes	
	CAPS Measure and Timepoint[b]	**Mean Change in CAPS per Arm (SEM or SD)** (Between Group Difference [BGD] and P-value vs Control Group, if provided)	**Response Measures**	**Proportion of Patients with Response (%)**

Manual of Mental Disorders; ITT, intention to treat; MDMA, 3,4-methylenedioxymethamphetamine; n, number; PBO, inert placebo; PTSD, post-traumatic stress disorder; SD, standard deviation; SEM, standard error of the mean

[a] This information was accompanied by a hypothesis test in the summary publication, but without appropriate meta-analytic techniques, the statistical comparisons are uninformative.

[b] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the original amount.

[c] The primary objective of the summary studies was either regarding outcomes related to sleep quality (Ponte et al) or to patient-reported personal growth in areas of self-perception, interpersonal relationships, and life-philosophy (Gorman et al). Authors did not capture all RCTs available with CAPS efficacy outcome (ie, pooled CAPS outcomes reported are not all-encompassing of the full range of RCTs available)

APPENDIX G – SERIOUS ADVERSE EVENTS (SAES)

Table G1. Serious Adverse Events Primarily during the Blinded Trial Period for Randomized Controlled Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[a]*	**SAEs[b]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
Mitchell 2021[32] NCT03537014 *Randomized: MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n = 45) Safety Analysis: MDMA 80-120 mg (n=46) for 3 sessions vs PBO (n =44)*	**SAEs from the first experimental session to study termination[32]**		
	Deaths	0 (0%)	0 (0%)
	Suicide attempts	0 (0%)	1 (2.3%)
	Suicidal ideation resulting in self-hospitalization	0 (0%)	1 (2.3%)
Unpublished [44] NCT01958593 *Terminated Early Randomized and Safety Analysis: MDMA 125 mg (n=4) for 2 sessions vs PBO (n=2)*	**SAEs during Stage 1 (blinded period) reported on ClinicalTrials.gov [44]**		
	Deaths	0 (0%)	0 (0%)
	SAEs	0 (0%)	0 (0%)
Unpublished [45] NCT01689740 *Randomized: MDMA 125 mg (n=5) for 2 sessions vs APBO 25 mg (n=3) Safety Analysis: MDMA 125 mg (n=7)[c] for 2 sessions vs APBO 25 mg (n=3)*	**SAEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[45]**		
	Deaths	0 (0%)	0 (0%)
	SAEs	0 (0%)	0 (0%)
Ot'alora 2018[46] NCT01793610 *Randomized and Safety Analysis: MDMA 125 mg (n= 13) or 100 mg (n= 9) for 2 sessions vs APBO 40 mg (n=6)*	**SAEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[52]**		
	Deaths	125 mg: 0 (0%)	0 (0%)
		100 mg: 0 (0%)	
	Breast cancer[d]	125 mg: 1 (7.7%)	0 (0%)
		100 mg: 0 (0%)	
	Lower limb fracture[d]	125 mg: 0 (0%)	0 (0%)

Table G1. Serious Adverse Events Primarily during the Blinded Trial Period for Randomized Controlled Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[a]*	**SAEs[b]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
		100 mg: 1 (11.1%)	
	Ruptured ovarian cyst[d]	125 mg: 0 (0%)	0 (0%)
		100 mg: 1 (11.1%)	
Mithoefer 2018[47] NCT01211405 *Randomized and Safety Analysis: MDMA 125 mg (n=12) or 75 mg (n=7) for 2 sessions, vs APBO 30 mg (n=7)*	**SAEs during the entire study period (ie, may include blinded and open-label periods when) reported on clincialtrials.gov[47]**		
	Deaths	0 (0%)	0 (0%)
	Ventricular extrasystole	75 mg: 0 (0%)	1 (14.3%) Occurred during open-label treatment with active MDMA dose[33]
		125 mg: 0 (0%)	
	Suicidal ideation and depression	75 mg: 0 (0%)	1 (14.3%)
		125 mg: 0 (0%)	
	Appendicitis	75 mg: 1 (14.3%)	0 (0%)
		125 mg: 0 (0%)	
Oehen 2013[48] NCT00353938 *Randomized and Safety Analysis: MDMA 125 mg (n=9) for 3 treatment sessions vs APBO 25 mg (n=5)*	**SAEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[54]**		
	Deaths	0 (0%) One participant died 6 months after MDMA treatment from a recurrence of breast cancer that had been in remission for >10 years.[48]	0 (0%)
	Metastases to CNS[e]	1 (11.1%)	0 (0%)
	Suicidal behavior[e]	1 (11.1%)	0 (0%)
Mithoefer 2011[49] NCT00090064 *Randomized and Safety Analysis: MDMA 125 mg (n=15) for 2 sessions vs PBO (n=8)*	**SAEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[55]**		
	Deaths	0 (0%)	0 (0%)
	Clavicle fracture[e]	1 (6.7%)	0 (0%)
	Syncope[e]	1 (6.7%)	0 (0%)

Table G1. Serious Adverse Events Primarily during the Blinded Trial Period for Randomized Controlled Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[a]*	**SAEs[b]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
Unpublished[43] NCT00402298 *Terminated Early* *Randomized and Safety Analysis:* *MDMA 125 mg (n= 3) for 2 treatment sessions vs APBO 25 mg (n=2)*	**SAEs from informed consent to study termination after 12 month follow up (ie, it may include the blinded and open-label follow-up periods) reported on ClinicalTrials.gov[43]**		
	Deaths	0 (0%)	0 (0%)
	SAEs	0 (0%)	0 (0%)

Abbreviations: APBO, active placebo; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PBO, inert placebo; PTSD, post-traumatic stress disorder; SAEs, serious adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] This table includes only SAEs that were collected only during the blinded treatment, and does not include SAEs that were collected during the open-label and/or follow-up period, if applicable. In general, SAEs were defined as events that resulted in death, were life-threatening, required or extended an inpatient hospitalization, caused significant incapacity/disability, resulted in congenital defects, or required an intervention to prevent permanent harm.

[c] Appears to include the participants that were randomized to MDMA 125 mg (n=5) plus the lead-in, open-label individuals (n=2), but it is unclear

[d] Although ClinicialTrials.gov suggests the event occurred during the blinded study period (Stage 1), the publication reported that 2 of the 3 events (ie, fractured lower limb, ruptured ovarian cyst) occurred during the 12-month follow-up, and the other event (breast cancer) occurred during the open-label period. None of the SAEs were considered to be related to the administration of MDMA,

[e] Events are reported as SAEs on ClinicalTrials.gov in contrast to the published article that stated no drug-related adverse events occurred. This may mean the SAEs were considered unrelated to MDMA therapy.

APPENDIX H – ADDITIONAL PSYCHIATRIC ADVERSE EVENTS INFORMATION

Table H1. Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	Psychiatric AEs[c]	Active MDMA Number of affected participants (%)	Control Number of affected participants (%)
Unpublished[44] NCT01958593 *Terminated Early* *Randomized and Safety Analysis: MDMA 125 mg (n=4) for 2 sessions vs PBO (n=2)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[44]**		
	Anxiety	**2 (50.0%)**	**0 (0%)**
	Bruxism	**1 (25.0%)**	**0 (0%)**
	Depressed mood	**2 (50.0%)**	**0 (0%)**
	Dissociation	**0 (0%)**	**1 (50%)**
	Emotional distress	**1 (25.0%)**	**1 (50.0%)**
	Insomnia	**1 (25.0%)**	**0 (0%)**
	Intentional self-injury	**0 (0%)**	**1 (50.0%)**
	Restlessness	**1 (25.0%)**	**0 (0%)**
Unpublished[45] NCT01689740 *Randomized: MDMA 125 mg (n=5) for 2 sessions vs APBO 25 mg (n=3)* *Safety Analysis: MDMA 125 mg (n=7)[d] for 2 sessions vs APBO 25 mg (n=3)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[45]**		
	Anger	0 (0%)	0 (0%)
	Anxiety	**4 (57.1%)**	**0 (0%)**
	Depression	**1 (14.3%)**	**0 (0%)**
	Insomnia	**0 (0%)**	**0 (0%)**
	Major depression	**1 (14.3%)**	**0 (0%)**
	Suicidal ideation	**1 (14.3%)**	**0 (0%)**
Ot'alora 2018[46] NCT01793610 *Randomized and Safety Analysis: MDMA 125 mg (n=13) or 100 mg (n=9) for 2 sessions vs APBO 40 mg (n=6)*	**TEAEs reported after the first dose administration to 1 month post 2nd experimental session/dose (primary endpoint, self-reported)[46]**		
	Anxiety	**125 mg: 4 (30.8%)**	**0 (0%)**
		100 mg: 3 (33.3%)	
	Depressed mood	**125 mg: 2 (15.4%)**	**0 (0%)**
		100 mg: 2 (22.2%)	
	Irritability	**125 mg: 1 (7.7%)**	**0 (0%)**
		100 mg: 2 (22.2%)	
	Obsessive rumination	**125 mg: 1 (7.7%)**	**0 (0%)**

Table H1. Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Psychiatric AEs[c]**	**Active MDMA** Number of affected participants (%)	**Control** Number of affected participants (%)
		100 mg: 1 (11.1%)	
	Panic attack	**125 mg: 1 (7.7%)**	0 (0%)
		100 mg: 0 (0%)	
	Restlessness	**125 mg: 0 (0%)**	0 (0%)
		100 mg: 1 (11.1%)	
	Expected AEs during blinded experimental sessions 1 and 2[46e]		
	Anxiety	**125 mg: 7 (53.8%)**	**2 (33.3%)**
		100 mg: 6 (66.7%)	
	Jaw clenching, tight jaw	**125 mg: 8 (61.5%)**	**2 (33.3%)**
		100 mg: 5 (55.6%)	
	Low mood	**125 mg: 2 (15.4%)**	**0 (0%)**
		100 mg: 5 (55.6%)	
	Expected AEs during the 7 days following the blinded experimental sessions 1 and 2[46e]		
	Anxiety	**125 mg: 10 (76.9%)**	**2 (33.3%)**
		100 mg: 8 (88.9%)	
	Difficulty concentrating	**125 mg: 2 (15.4%)**	**2 (33.3%)**
		100 mg: 5 (55.6%)	
	Increased irritability	**125 mg: 6 (46.2%)**	**2 (33.3%)**
		100 mg: 5 (55.6%)	
	Insomnia	**125 mg: 6 (46.2%)**	**3 (50.0%)**
		100 mg: 7 (77.8%)	
	Low mood	**125 mg: 9 (69.2%)**	**2 (33.3%)**
		100 mg: 6 (66.7%)	
	Ruminations	**125 mg: 6 (46.2%)**	**1 (16.7%)**
		100 mg: 5 (55.6%)	
Mithoefer 2018[47] NCT01211405 *Randomized and Safety Analysis: MDMA 125 mg*	**TEAEs reported after the first dose administration to the day before the third experimental session (self-reported)[47]**		
	Anxiety	**125 mg: 1 (8.0%)**	**1 (14.0%)**
		75 mg: 0 (0%)	

Table H1. Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Psychiatric AEs[c]**	**Active MDMA** Number of affected participants (%)	**Control** Number of affected participants (%)
(n=12) or 75 mg (n=7) for 2 sessions, vs APBO 30 mg (n=7)	**Flashbacks**	**125 mg: 1 (8.0%)**	**0 (0%)**
		75 mg: 0 (0%)	
	Low mood	**125 mg: 0 (0%)**	**2 (29.0%)**
		75 mg: 0 (0%)	
	Negative thoughts	**125 mg: 0 (0%)**	**1 (14.0%)**
		75 mg: 0 (0%)	
	Suicidal ideation	**125 mg: 0 (0%)**	**1 (14.0%)**
		75 mg: 0 (0%)	
	Tic	**125 mg: 1 (8.0%)**	**0 (0%)**
		75 mg: 0 (0%)	
	Trichotillomania	**125 mg: 0 (0%)**	**1 (14.0%)**
		75 mg: 0 (0%)	
	Expected AEs during blinded experimental sessions 1 and 2[47e]		
	Anxiety	**125 mg: 11 (92.0%)**	**4 (57.0%)**
		75 mg: 6 (86.0%)	
	Jaw clenching or tight jaw	**125 mg: 9 (75.0%)**	**0 (0%)**
		75 mg: 4 (57.0%)	
	Restlessness	**125 mg: 3 (25.0%)**	**4 (57.0%)**
		5 (71.0%)	
	Expected AEs during the 7 days following the blinded experimental sessions 1 and 2[47e]		
	Anxiety	**125 mg: 10 (83.0%)**	**4 (57.0%)**
		75 mg: 5 (71.0%)	
	Difficulty concentrating	**125 mg: 5 (42.0%)**	**2 (29.0%)**
		75 mg: 0 (0%)	
	Increased irritability	**125 mg: 6 (50.0%)**	**4 (57.0%)**
		75 mg: 2 (29.0%)	
	Insomnia	**125 mg: 10 (83.0%)**	**5 (71.0%)**
		75 mg: 3 (43.0%)	

Table H1. Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Psychiatric AEs[c]**	**Active MDMA** Number of affected participants (%)	**Control** Number of affected participants (%)
	Low mood	**125 mg: 3 (25.0%)**	**3 (43.0%)**
		75 mg: 0 (0%)	
Oehen 2013[48] NCT00353938 *Randomized and Safety Analysis: MDMA 125 mg (n=9) for 3 treatment sessions vs APBO 25 mg (n=5)*	AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[54]		
	Anxiety	**4 (44.4%)**	**1 (20.0%)**
	Depressed mood	**2 (22.2%)**	**0 (0%)**
	Disturbance in attention	**2 (22.2%)**	**0 (0%)**
	Insomnia	**2 (22.2%)**	**1 (20.0%)**
	Intentional self-injury	0 (0%)	1 (20.0%)
	Panic attack	**1 (11.1%)**	**0 (0%)**
	Somatoform disorder	**1 (11.1%)**	**0 (0%)**
	Somnolence	**1 (11.1%)**	**0 (0%)**
	Suicidal behavior	**1 (11.1%)**	**0 (0%)**
	Tension	**1 (11.1%)**	**0 (0%)**
Mithoefer 2011[49] NCT00090064 *Randomized and Safety Analysis: MDMA 125 mg (n=15) for 2 sessions vs PBO (n=8)*	AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[55]		
	Agitation	0 (0%)	0 (0%)
	Anxiety	**2 (13.3%)**	**4 (50.0%)**
	Bruxism	**1 (6.7%)**	**0 (0%)**
	Depressed mood	**1 (6.7%)**	**1 (12.5%)**
	Derealization	**1 (6.7%)**	**0 (0%)**
	Dissociation	**1 (6.7%)**	**0 (0%)**
	Disturbance in attention	**1 (6.7%)**	**0 (0%)**
	Flashback	0 (0%)	0 (0%)
	Insomnia	**0 (0%)**	**1 (12.5%)**
	Major depression	**1 (6.7%)**	**0 (0%)**
	Memory impairment	**0 (0%)**	**1 (12.5%)**
	Panic attack	**1 (6.7%)**	**0 (0%)**
Unpublished[43] NCT00402298 *Terminated Early*	Psychiatric AEs were not reported during the blinded treatment phase for each arm on ClinicalTrials.gov[43]		

Table H1. Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Psychiatric AEs[c]**	**Active MDMA** Number of affected participants (%)	**Control** Number of affected participants (%)
Randomized and Safety Analysis: MDMA 125 mg (n= 3) for 2 treatment sessions vs APBO 25 mg (n=2)			

Abbreviations: AEs, adverse events; APBO, active placebo; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PBO, inert placebo; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] Psychiatric AEs from the phase 3 clinical trial (NCT03537014) are reported in **Table 7** in the text.

[b] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[c] Psychiatric AEs that were collected only during the blinded treatment segments are reported, and does not include adverse events that were collected during the open-label and/or follow-up period, if applicable. Keep in mind that "treatment-emergent" AE could be defined differently among studies and the events may or may not have been considered drug-related.

[d] Appears to include the participants that were randomized to MDMA 125 mg (n=5) plus the lead-in, open-label individuals (n=2), but it is unclear

[e] Participants that reported an expected, spontaneously reported adverse event by ≥40% in at least one group

Table H2. Frequency of Psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis*[a]	**Psychiatric AEs**[b]	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
Mithoefer 2019[33] NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610 *Randomized and Safety Analysis: MDMA 75-125 mg (n=72) for 2 sessions vs Comparator (MDMA 0-40 mg) (n=31)*	**Expected AEs reported during the 7 days following the blinded experimental sessions 1 and 2**[b]		
	Anxiety	**Day 1**	
		21 (29.2%)	**7 (22.6%)**
		Day 2	
		31 (43.1%)	13 (41.9%)
		Day 3	
		35 (48.6%)	**12 (38.7%)**
		Day 4	
		25 (34.7%)	**13 (41.9%)**
		Day 5	
		27 (37.5%)	13 (41.9%)
		Day 6	
		32 (44.4%)	**11 (35.5%)**
		Day 7	
		19 (26.4%)	7 (22.6%)
	Difficulty concentrating	**Day 1**	
		5 (6.9%)	**5 (16.1%)**
		Day 2	
		7 (9.7%)	**5 (16.1%)**
		Day 3	
		10 (13.9%)	4 (12.9%)
		Day 4	
		7 (9.7%)	3 (9.7%)
		Day 5	
		9 (12.5%)	4 (12.9%)

Table H2. Frequency of Psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis*[a]	**Psychiatric AEs**[b]	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		Day 6	
		9 (12.5%)	4 (12.9%)
		Day 7	
		6 (8.3%)	**1 (3.2%)**
	Insomnia	**Day 1**	
		34 (47.2%)	**11 (35.5%)**
		Day 2	
		20 (27.8%)	**11 (35.5%)**
		Day 3	
		21 (29.2%)	**11 (35.5%)**
		Day 4	
		16 (22.2%)	**9 (29.0%)**
		Day 5	
		19 (26.4%)	9 (29.0%)
		Day 6	
		13 (18.1%)	**13 (41.9%)**
		Day 7	
		8 (11.1%)	**6 (19.4%)**
	Jaw clenching, tight jaw	**Day 1**	
		16 (22.2%)	**0 (0%)**
		Day 2	
		10 (13.9%)	**2 (6.5%)**
		Day 3	
		1 (1.4%)	1 (3.2%)
		Day 4	
		6 (8.3%)	2 (6.5%)

Table H2. Frequency of Psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis*[a]	**Psychiatric AEs**[b]	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		Day 5	
		4 (5.6%)	2 (6.5%)
		Day 6	
		3 (4.2%)	1 (3.2%)
		Day 7	
		5 (6.9%)	1 (3.2%)
	Low mood	**Day 1**	
		17 (23.6%)	**4 (12.9%)**
		Day 2	
		25 (34.7%)	**6 (19.4%)**
		Day 3	
		19 (26.4%)	**6 (19.4%)**
		Day 4	
		24 (33.3%)	**8 (25.8%)**
		Day 5	
		19 (26.4%)	8 (25.8%)
		Day 6	
		13 (18.1%)	7 (22.6%)
		Day 7	
		12 (16.7%)	4 (12.9%)
	Restlessness	**Day 1**	
		8 (11.1%)	3 (9.7%)
		Day 2	
		6 (8.3%)	**1 (3.2%)**
		Day 3	
		4 (5.6%)	1 (3.2%)

Table H2. Frequency of Psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis*[a]	**Psychiatric AEs**[b]	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		Day 4	
		6 (8.3%)	**0 (0%)**
		Day 5	
		5 (6.9%)	2 (6.5%)
		Day 6	
		7 (9.7%)	**1 (3.2%)**
		Day 7	
		3 (4.2%)	0 (0%)

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[b] Only the psychiatric AEs with a ≥5% difference between the MDMA active group and the control group during the blinded experimental sessions 1 and 2 were reported for the seven days following.

APPENDIX I – ADDITIONAL NON-PSYCHIATRIC ADVERSE EVENTS INFORMATION

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
Unpublished[44] NCT01958593 *Terminated Early* *Randomized and Safety Analysis: MDMA 125 mg (n=4) for 2 sessions vs PBO (n=2)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[44]**		
	Concussion	**0 (0%)**	**0 (0%)**
	Fatigue	**1 (25.0%)**	**0 (0%)**
	Headache	**1 (25.0%)**	**0 (0%)**
	Muscle tightness	**1 (25.0%)**	**0 (0%)**
	Nausea	**1 (25.0%)**	**0 (0%)**
	Pain	**1 (25.0%)**	**0 (0%)**
	Paresthesia	**1 (25.0%)**	**0 (0%)**
Unpublished[45] NCT01689740 *Randomized: MDMA 125 mg (n=5) for 2 sessions vs APBO 25 mg (n=3)* *Safety Analysis: MDMA 125 mg (n=7)[d] for 2 sessions vs APBO 25 mg (n=3)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov[45]**		
	Asthma	0 (0%)	0 (0%)
	Dizziness	**2 (28.6%)**	**0 (0%)**
	Headache	**1 (14.3%)**	**0 (0%)**
	Hypersensitivity	0 (0%)	0 (0%)
	Influenza	**1 (14.3%)**	**1 (33.3%)**
	Intestinal obstruction	**1 (14.3%)**	**0 (0%)**
	Nausea	**1 (14.3%)**	**0 (0%)**
	Oropharyngeal pain	0 (0%)	0 (0%)
	Pyrexia	**1 (14.3%)**	**0 (0%)**
	Tremor	0 (0%)	0 (0%)
	Upper respiratory tract infection	**1 (14.3%)**	**0 (0%)**
Ot'alora 2018[46] NCT01793610	**Expected AEs during blinded experimental sessions 1 and 2[e]**		
	Dizziness	**125 mg: 7 (53.8%)**	**1 (16.7%)**
		100 mg: 2 (22.2%)	

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
Randomized and Safety Analysis: MDMA 125 mg (n= 13) or 100 mg (n= 9) for 2 sessions vs APBO 40 mg (n=6)	**Fatigue**	125 mg: 4 (30.8%)	**2 (33.3%)**
		100 mg: 4 (44.4%)	
	Headache	**125 mg: 3 (23.1%)**	**4 (66.7%)**
		100 mg: 4 (44.4%)	
	Muscle tension	**125 mg: 7 (53.8%)**	**2 (33.3%)**
		100 mg: 4 (44.4%)	
	Expected AEs reported during the 7 days following the blinded experimental sessions 1 and 2[e]		
	Fatigue	**125 mg: 9 (69.2%)**	**2 (33.3%)**
		100 mg: 7 (77.8%)	
	Headache	**125 mg: 5 (38.5%)**	**4 (66.7%)**
		100 mg: 3 (33.3%)	
	Lack of appetite	**125 mg: 8 (61.5%)**	**1 (16.7%)**
		100 mg: 1 (11.1%)	
	Muscle tension	**125 mg: 6 (46.2%)**	**2 (33.3%)**
		100 mg: 1 (11.1%)	
	Nausea	**125 mg: 8 (61.5%)**	**1 (16.7%)**
		100 mg: 3 (33.3%)	
	Need more sleep	**125 mg: 8 (61.5%)**	**2 (33.3%)**
		100 mg: 5 (55.6%)	
Mithoefer 2018[47] NCT01211405 *Randomized and Safety Analysis: MDMA 125 mg (n=12) or 75 mg (n=7) for 2 sessions, vs APBO 30 mg (n=7)*	**Expected AEs during blinded experimental sessions 1 and 2[e]**		
	Fatigue	**125 mg: 7 (58.0%)**	**5 (71.0%)**
		75 mg: 4 (57.0%)	
	Headache	125 mg: 8 (67.0%)	5 (71.0%)
		75 mg: 5 (71.0%)	
	Muscle tension	**125 mg: 9 (75.0%)**	**4 (57.0%)**

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
		75 mg: 3 (43.0%)	
	Perspiration	**125 mg: 5 (42.0%)**	**2 (29.0%)**
		75 mg: 2 (29.0%)	
	Reduced appetite	**125 mg: 8 (67.0%)**	**3 (43.0%)**
		75 mg: 4 (57.0%)	
	Sensitivity to cold	**125 mg: 6 (50.0%)**	**4 (57.0%)**
		75 mg: 4 (57.0%)	
	Expected AEs during the 7 days following the blinded experimental sessions 1 and 2[e]		
	Fatigue	125 mg: 10 (83.0%)	**6 (86.0%)**
		75 mg: 7 (100.0%)	
	Headache	**125 mg: 7 (58.0%)**	**2 (29.0%)**
		75 mg: 3 (43.0%)	
	Lack of appetite	**125 mg: 6 (50.0%)**	**2 (29.0%)**
		75 mg: 1 (14.0%)	
	Muscle tension	**125 mg: 7 (58.0%)**	**2 (29.0%)**
		75 mg: 3 (43.0%)	
	Need more sleep	**125 mg: 9 (75.0%)**	**6 (86.0%)**
		75 mg: 6 (86.0%)	
Oehen 2013[48] NCT00353938 *Randomized and Safety Analysis: MDMA 125 mg (n=9) for 3 treatment sessions vs APBO 25 mg (n=5)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov**[54]		
	Abdominal pain	**1 (11.1%)**	**0 (0%)**
	Angina tonsillitis	0 (0%)	0 (0%)
	Bronchial disorder	**0 (0%)**	**1 (20.0%)**
	Decreased appetite	**1 (11.1%)**	**0 (0%)**
	Diarrhea	**1 (11.1%)**	**0 (0%)**
	Dizziness	**1 (11.1%)**	**0 (0%)**
	Dyspnea	**1 (11.1%)**	**0 (0%)**

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
	Fatigue	**1 (11.1%)**	**2 (40.0%)**
	Headache	**1 (11.1%)**	**1 (20.0%)**
	Hypertension	**1 (11.1%)**	**0 (0%)**
	Hypothyroidism	**1 (11.1%)**	**0 (0%)**
	Increased erythrocyte sedimentation rate	**1 (11.1%)**	**0 (0%)**
	Iron deficiency anemia	0 (0%)	0 (0%)
	Limb injury	**1 (11.1%)**	**0 (0%)**
	Lower abdominal pain	**1 (11.1%)**	**0 (0%)**
	Nausea	**1 (11.1%)**	**0 (0%)**
	Neck pain	0 (0%)	0 (0%)
	Muscle spasms	0 (0%)	0 (0%)
	Otitis media	**0 (0%)**	**1 (20.0%)**
	Pain	**0 (0%)**	**1 (20.0%)**
	Pneumonia	**1 (11.1%)**	**0 (0%)**
	Pneumonia (chlamydial)	**1 (11.1%)**	**0 (0%)**
	Psoriasis	**1 (11.1%)**	**0 (0%)**
	Reduced visual acuity	**1 (11.1%)**	**0 (0%)**
	Urinary tract infection	0 (0%)	0 (0%)
	Vomiting	**1 (11.1%)**	**0 (0%)**
Mithoefer 2011[49] NCT00090064 *Randomized and Safety Analysis: MDMA 125 mg (n=15) for 2 sessions vs PBO (n=8)*	**AEs during Stage 1 (blinded period) reported on ClinicalTrials.gov**[55]		
	Anorexia	**1 (6.7%)**	**0 (0%)**
	Arthralgia	**0 (0%)**	**1 (12.5%)**
	Back pain	**1 (6.7%)**	**1 (12.5%)**
	Blurred vision	**1 (6.7%)**	**0 (0%)**
	Burning sensation	**1 (6.7%)**	**1 (12.5%)**

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
	Chills	**1 (6.7%)**	**0 (0%)**
	Dermatitis	0 (0%)	0 (0%)
	Diarrhea	**3 (20.0%)**	**1 (12.5%)**
	Dizziness	**1 (6.7%)**	**0 (0%)**
	Dyspepsia	**1 (6.7%)**	**0 (0%)**
	Dysuria	**1 (6.7%)**	**0 (0%)**
	Facial pain	**0 (0%)**	**1 (12.5%)**
	Fatigue	**4 (26.7%)**	**1 (12.5%)**
	Feeling hot	**2 (13.3%)**	**0 (0%)**
	Gastric ulcer	0 (0%)	0 (0%)
	Headache	**1 (6.7%)**	**0 (0%)**
	Hypoesthesia facial	**1 (6.7%)**	**0 (0%)**
	Influenza-like illness	**1 (6.7%)**	**0 (0%)**
	Irritability	**2 (13.3%)**	**0 (0%)**
	Laryngitis	**1 (6.7%)**	**0 (0%)**
	Muscle spasms	**1 (6.7%)**	**1 (12.5%)**
	Muscle strain	**1 (6.7%)**	**0 (0%)**
	Muscle tightness	**5 (33.3%)**	**1 (12.5%)**
	Musculoskeletal chest pain	**0 (0%)**	**2 (25.0%)**
	Musculoskeletal pain	2 (13.3%)	1 (12.5%)
	Myalgia	0 (0%)	0 (0%)
	Myoclonus	**1 (6.7%)**	**0 (0%)**
	Nausea	**1 (6.7%)**	**0 (0%)**
	Neck pain	**1 (6.7%)**	**1 (12.5%)**
	Nocturia	**1 (6.7%)**	**0 (0%)**
	Oropharyngeal blistering	**1 (6.7%)**	**0 (0%)**

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
	Oropharyngeal pain	**1 (6.7%)**	**0 (0%)**
	Otitis media	**0 (0%)**	**1 (12.5%)**
	Ovarian cyst	**1 (6.7%)**	**0 (0%)**
	Pain	**1 (6.7%)**	**1 (12.5%)**
	Pain in extremity	**0 (0%)**	**1 (12.5%)**
	Palpitations	0 (0%)	0 (0%)
	Pharyngitis	**0 (0%)**	**1 (12.5%)**
	Pharyngitis (streptococcal)	**1 (6.7%)**	**0 (0%)**
	Pruritus	**0 (0%)**	**1 (12.5%)**
	Sciatica	**0 (0%)**	**1 (12.5%)**
	Sinusitis	**1 (6.7%)**	**0 (0%)**
	Sinus headache	**1 (6.7%)**	**0 (0%)**
	Sinus tachycardia	**1 (6.7%)**	**0 (0%)**
	Tension headache	**1 (6.7%)**	**0 (0%)**
	Throat tightness	**0 (0%)**	**1 (12.5%)**
	Upper abdominal pain	**0 (0%)**	**1 (12.5%)**
	Upper respiratory tract infection	2 (13.3%)	1 (12.5%)
	Urinary tract infection	**1 (6.7%)**	**0 (0%)**
	Visual impairment	2 (13.3%)	1 (12.5%)
	Vomiting	**1 (6.7%)**	**0 (0%)**
	Weakness (asthenia)	**1 (6.7%)**	**0 (0%)**
Unpublished[43] NCT00402298 *Terminated Early*	**AEs reported from study start to 12 month follow-up (ie, including the blinded and open-label period) by ClinicalTrials.gov[f]**		
	Vomiting	**1 (33.3%)**	**0 (0%)**
	Flatulence	**1 (33.3%)**	**0 (0%)**

Table I1. Non-Psychiatric Adverse Events from the Blinded Trial Period for Additional[a] Included Randomized Controlled Trials of MDMA-assisted Therapy for PTSD

Study (first author, publication year) NCT *Comparison and number of participants in the analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA** Number of affected patients (%)	**Control** Number of affected patients (%)
Randomized and Safety Analysis: MDMA 125 mg (n= 3) for 2 treatment sessions vs APBO 25 mg (n=2)	**Fasciculation**	**1 (33.%)**	**1 (50%)**
	Myoclonus	**0 (0%)**	**1 (50%)**
	Viral upper respiratory tract infection	**0 (0%)**	**1 (50%)**

Abbreviations: AEs, adverse events; APBO, active placebo; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PBO, inert placebo; PTSD, post-traumatic stress disorder; TEAEs, treatment-emergent adverse events

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[a] Non-psychiatric AEs from the phase 3 clinical trial (NCT03537014) are reported in **Table 9** in the text.

[b] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[c] Only non-psychiatric AEs that were collected during the blinded treatment segments are reported (ie, not including any open-label follow-up period). Keep in mind that "treatment-emergent" AE could be defined differently among studies and the events may or may not have been considered drug-related

[d] Appears to include the participants that were randomized to MDMA 125 mg (n=5) plus the lead-in, open-label individuals (n=2), but it is unclear

[e] Participants that reported an expected, spontaneously reported adverse event by ≥40% in at least one group

[f] Reporting from this trial was considered unreliable by investigators.

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
Mithoefer 2019[33] NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610 *Randomized and Safety Analysis: MDMA 75-125 mg (n=72) for 2 sessions vs Comparator (MDMA 0-40 mg) (n=31)*	**Expected reactions reported during the 7 days following the blinded experimental sessions 1 and 2[d, e]**		
	Dizziness	**Day 1**	
		5 (6.9%)	3 (9.7%)
		Day 2	
		8 (11.1%)	**2 (6.5%)**
		Day 3	
		6 (8.3%)	2 (6.5%)
		Day 4	
		6 (8.3%)	**0 (0%)**
		Day 5	
		5 (6.9%)	1 (3.2%)
		Day 6	
		6 (8.3%)	**0 (0%)**
		Day 7	
		3 (4.2%)	0 (0%)
	Fatigue	**Day 1**	
		43 (59.7%)	**17 (54.8%)**
		Day 2	
		34 (47.2%)	**12 (38.7%)**
		Day 3	
		28 (38.9%)	**10 (32.3%)**
		Day 4	
		23 (31.9%)	11 (35.5%)
		Day 5	
		22 (30.6%)	**11 (35.5%)**
		Day 6	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		23 (31.9%)	10 (32.3%)
		Day 7	
		9 (12.5%)	**8 (25.8%)**
	Headache	**Day 1**	
		17 (23.6%)	**11 (35.5%)**
		Day 2	
		10 (13.9%)	5 (16.1%)
		Day 3	
		6 (8.3%)	3 (9.7%)
		Day 4	
		8 (11.1%)	3 (9.7%)
		Day 5	
		6 (8.3%)	2 (6.5%)
		Day 6	
		8 (11.1%)	**2 (6.5%)**
		Day 7	
		3 (4.2%)	2 (6.5%)
	Heavy leg	**Day 1**	
		2 (2.8%)	0 (0%)
		Day 2	
		1 (1.4%)	0 (0%)
		Day 3	
		0 (0%)	0 (0%)
		Day 4	
		0 (0%)	0 (0%)
		Day 5	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		0 (0%)	0 (0%)
		Day 6	
		1 (1.4%)	0 (0%)
		Day 7	
		0 (0%)	0 (0%)
	Impaired gait/balance	**Day 1**	
		3 (4.2%)	0 (0%)
		Day 2	
		0 (0%)	0 (0%)
		Day 3	
		1 (1.4%)	1 (3.2%)
		Day 4	
		1 (1.4%)	0 (0%)
		Day 5	
		1 (1.4%)	0 (0%)
		Day 6	
		2 (2.8%)	0 (0%)
		Day 7	
		0 (0%)	0 (0%)
	Lack of appetite	**Day 1**	
		20 (27.8%)	**5 (16.1%)**
		Day 2	
		17 (23.6%)	**3 (9.7%)**
		Day 3	
		11 (15.3%)	**3 (9.7%)**
		Day 4	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		10 (13.9%)	**1 (3.2%)**
		Day 5	
		7 (9.7%)	**1 (3.2%)**
		Day 6	
		9 (12.5%)	**1 (3.2%)**
		Day 7	
		6 (8.3%)	**0 (0%)**
	Muscle tension	**Day 1**	
		15 (20.8%)	7 (22.6%)
		Day 2	
		16 (22.2%)	**4 (12.9%)**
		Day 3	
		8 (11.1%)	3 (9.7%)
		Day 4	
		7 (9.7%)	2 (6.5%)
		Day 5	
		7 (9.7%)	4 (12.9%)
		Day 6	
		6 (8.3%)	3 (9.7%)
		Day 7	
		5 (6.9%)	3 (9.7%)
	Nausea	**Day 1**	
		15 (20.8%)	**4 (12.9%)**
		Day 2	
		13 (18.1%)	**3 (9.7%)**
		Day 3	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		9 (12.5%)	4 (12.9%)
		Day 4	
		6 (8.3%)	**1 (3.2%)**
		Day 5	
		7 (9.7%)	2 (6.5%)
		Day 6	
		5 (6.9%)	**0 (0%)**
		Day 7	
		3 (4.2%)	0 (0%)
	Need more sleep	**Day 1**	
		17 (23.6%)	6 (19.4%)
		Day 2	
		25 (34.7%)	**7 (22.6%)**
		Day 3	
		13 (18.1%)	**4 (12.9%)**
		Day 4	
		14 (19.4%)	7 (22.6%)
		Day 5	
		8 (11.1%)	**6 (19.4%)**
		Day 6	
		8 (11.1%)	**7 (22.6%)**
		Day 7	
		4 (5.6%)	**6 (19.4%)**
	Nystagmus	**Day 1**	
		0 (0%)	0 (0%)
		Day 2	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		0 (0%)	0 (0%)
		Day 3	
		0 (0%)	0 (0%)
		Day 4	
		0 (0%)	0 (0%)
		Day 5	
		0 (0%)	0 (0%)
		Day 6	
		0 (0%)	0 (0%)
		Day 7	
		0 (0%)	0 (0%)
	Paresthesia	**Day 1**	
		1 (1.4%)	0 (0%)
		Day 2	
		1 (1.4%)	0 (0%)
		Day 3	
		0 (0%)	0 (0%)
		Day 4	
		1 (1.4%)	0 (0%)
		Day 5	
		0 (0%)	0 (0%)
		Day 6	
		1 (1.4%)	0 (0%)
		Day 7	
		1 (1.4%)	0 (0%)
	Perspiration	**Day 1**	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		3 (4.2%)	1 (3.2%)
		Day 2	
		0 (0%)	0 (0%)
		Day 3	
		1 (1.4%)	1 (3.2%)
		Day 4	
		0 (0%)	0 (0%)
		Day 5	
		0 (0%)	0 (0%)
		Day 6	
		0 (0%)	0 (0%)
		Day 7	
		0 (0%)	0 (0%)
	Sensitivity to cold	**Day 1**	
		3 (4.2%)	2 (6.5%)
		Day 2	
		3 (4.2%)	0 (0%)
		Day 3	
		3 (4.2%)	0 (0%)
		Day 4	
		3 (4.2%)	0 (0%)
		Day 5	
		1 (1.4%)	1 (3.2%)
		Day 6	
		1 (1.4%)	1 (3.2%)
		Day 7	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		0 (0%)	0 (0%)
	Thirst	**Day 1**	
		4 (5.6%)	1 (3.2%)
		Day 2	
		1 (1.4%)	0 (0%)
		Day 3	
		0 (0%)	0 (0%)
		Day 4	
		0 (0%)	0 (0%)
		Day 5	
		0 (0%)	0 (0%)
		Day 6	
		0 (0%)	0 (0%)
		Day 7	
		0 (0%)	0 (0%)
	Weakness	**Day 1**	
		2 (2.8%)	1 (3.2%)
		Day 2	
		7 (9.7%)	2 (6.5%)
		Day 3	
		4 (5.6%)	**0 (0%)**
		Day 4	
		2 (2.8%)	0 (0%)
		Day 5	
		4 (5.6%)	**0 (0%)**
		Day 6	

Table I2. Non-psychiatric Adverse Events from During the 7 Days Following Blinded Dosing Sessions from the Summary Study of Phase 2 Trials of MDMA-assisted Therapy for PTSD[a]

Study (first author, publication year) NCT *Comparison and number of participants in analysis[b]*	**Non-psychiatric AEs[c]**	**Active MDMA (Initial Dose of 75-125 mg)** Number of affected patients (%)	**Control (Initial MDMA Dose of 0-40 mg)** Number of affected patients (%)
		2 (2.8%)	0 (0%)
		Day 7	
		2 (2.8%)	0 (0%)

Abbreviations: AEs, adverse events; MDMA, 3,4-methylenedioxymethamphetamine; NCT, National Clinical Trial; PTSD, post-traumatic stress disorder

Bold text indicates approximately a ≥5% difference between the MDMA active group and the comparator/control group

[b] In all studies, both the active-dose MDMA arm and comparator arm received identical psychotherapy. Note that doses reported are based on the initial dose used during experimental therapy sessions. Most participants also received an additional dose of half the initial amount.

[c] Non-psychiatric AEs that were collected only during the blinded treatment segments are reported, and does not include adverse events that were collected during the open-label and/or follow-up period, if applicable..

[d] Participants that reported an expected, spontaneously reported adverse event

[e] Only the non-psychiatric AEs with a ≥5% difference between the MDMA active group and the comparator/control group during the blinded experimental sessions 1 and 2 were reported for the seven days following

APPENDIX J – RISK OF BIAS ASSESSMENT

Table J1. Explanation for Risk of Bias Ratings for the Domain-based Risk of Bias Assessment

Study	Allocation sequence generation	Allocation sequence concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data (attrition)	Selective reporting	Total Jadad Score
Mitchell et al. 2021 *Nat Med* (NCT03537014) 32,50,60	**Low**	**Low**	**High**	**High**	**Low**	**High**	**High**	Jadad score = 3
	Jadad score = 2		Jadad score = 1			Jadad score = 0		
	Allocation was centrally conducted and stratified by site using an Interactive Web Randomization System (IWRS), which suggests that allocation was determined using a random component.	Allocation was conducted with a third-party IWRS that was locked to investigators except for an emergency, which allowed allocation to remain concealed.	Despite appropriate blinding techniques, it may have been compromised due to effects associated with MDMA treatment. Approximately 90% of subjects overall guess their treatment assignment, including approximately 96% of MDMA subjects and 84% of placebo participants [per publication].	Despite blinding, those clinicians delivering the interventions were likely able to guess subject treatment assignment. There was not a formal or informal assessment (eg, allocation guesses), so this is extrapolated from the data on participants' guesses of treatment assignment.	A centralized pool of independent outcome assessors was used to assess the primary and secondary efficacy outcome measures (ie, CAPS-5 and SDS).	Overall concern: We are unable to discern how many participants had complete outcome data for the "de facto" and "de jure" estimands. The investigators reported they did not perform any imputation of outcomes, and they imply that they included all participants (except for those noted below) despite also reporting that 8 of 90 (4 MDMA and 4 placebo participants; 8.8%) were missing data for the primary endpoint. We tracked the following reporting of attrition, per the investigators, but it does not account for the fact that up to 11 participants (8 with final outcome and 3 with other missing data) appear to be missing outcome measurements: 1. For the mITT ("de facto") estimand (1.1% overall attrition; 0% MDMA and 2.2% placebo) due to 1 placebo participant withdrawal before treatment without reason, but still completing CAPS-5 measurements. 2. For the "de jure" estimand (2.2% overall attrition; 0% MDMA and 4.4% placebo). Same concerns as "de facto" estimand, plus 1 placebo withdrew because of an unspecified AE.	Concerns due to: (1) inappropriate over-emphasis on reporting the efficacy results from the PP analysis set instead of the mITT analysis (eg, only reporting the PP difference on ClinicalTrials.gov and in the abstract); (2) lack of reporting all safety outcomes, including those that might favor the placebo arm (eg, infections reported on ClinicalTrials.gov but not mentioned in the published report); and (3) under-reporting the true mITT analysis (eg, only a P-value and Cohen's d reported for the mITT "de facto" estimand, lacking the numerical mean difference between treatment arms).	

Abbreviations: AE, adverse event; CAPS-5(4), Clinician-administered PTSD Scale for DSM-5(4); DSM-5(4), Diagnostic and Statistical Manual of Mental Disorders, 5th(4th) edition; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; IWRS, Interactive Web Randomization System; MDMA, 3,4-Methylenedioxymethamphetamine; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias; SAE, serious adverse events; SD, standard deviation; SDS, Sheehan Disability Scale; SOC, States of Consciousness questionnaire.

a. Based on primary blinded study period assessing primary outcome.

Table J1. Explanation for Risk of Bias Ratings for the Domain-based Risk of Bias Assessment

Study	Allocation sequence generation	Allocation sequence concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data (attrition)	Selective reporting	Total Jadad Score
						3. PP analysis (13.2% overall attrition; 8.7% MDMA, 17.8% placebo): Four additional placebo participants excluded without a reason. Three MDMA withdrawals without a reason, and 1 withdrawal because they "felt cured." Differential attrition risk.		
Unpublished report ClinicalTrials.gov (NCT01958593) [44,59]	**Unclear**	**Low**	**Unclear**	**Unclear**	**Low**	**Low**	**Unclear**	Jadad score = 5[a]
	Jadad score = 1		Jadad score = 2[a]			Jadad score = 1		
	Allocation was performed by an "unblinded randomization monitor," but there was insufficient information about the method used to generate the allocation sequence.	From the protocol, it appears a secure, separate system was used to maintain randomization codes. Blinded personnel (ie, everyone except the randomization monitor and pharmacist) entered the participant's participant number into a web-based program to identify the unique container corresponding to the participant's allocation.	Participants described as blinded until after the primary outcome evaluation. There is insufficient information to assess blinding success.	Personnel described as blinded until after the primary outcome evaluation. There is insufficient information to assess blinding success.	Independent outcome assessors (eg, lacking contact with participants during dosing sessions) were used to assess the primary outcome measure (CAPS-4).	Based on the limited information on ClinicalTrials.gov, all participants enrolled in the study were included in the analysis. Apparent attrition was 0%; 6 of 6 participants described as included in the analysis.	Comparing information reported on ClinicalTrials.gov to the study protocol, there are not overt discrepancies in the number of participants reported (the protocol did plan to enroll more participants, but ClinicalTrials.gov states the study was terminated early). However, ClinicalTrials.gov does not report secondary efficacy outcomes, the population used for the primary efficacy analysis, and some of the safety outcomes (eg, vital signs, suicidality). Of note, this study was included in some pooled analyses, which did report some of these outcomes in aggregate but lacked sufficient detail to assess reporting for this study alone.	
Unpublished report ClinicalTrials.gov (NCT01689740) [45,51]	**Unclear**	**Low**	**High**	**High**	**Low**	**Low**	**Unclear**	Jadad score = 2[a]
	Jadad score = 1		Jadad score = 0[a]			Jadad score = 1		
	Allocation was performed by an "unblinded randomization monitor," but there was insufficient information about the	From the protocol, it appears a web-based system was used to maintain randomization codes. Blinded personnel received an enrollment	The first 2 participants (20% of the total participants, and 28.5% of participants in the active MDMA arm) were enrolled in the open-label, full-dose lead-in of this pilot study, in an effort to review and	The first 2 participants (20% of the total participants, and 28.5% of participants in the active MDMA arm) were enrolled in the open-label, full-dose lead-in of this pilot study, in an effort to review and	Independent outcome assessors assessed the primary outcome measure (CAPS-4) and secondary efficacy measures. The protocol	Based on the limited information on ClinicalTrials.gov, all participants enrolled in this pilot study (10) were included in the analysis for each reported outcome measure,	Comparing information reported on ClinicalTrials.gov to this pilot study's protocol, there are not overt discrepancies in the number of participants enrolled (10), or the primary or secondary efficacy	

Abbreviations: AE, adverse event; CAPS-5(4), Clinician-administered PTSD Scale for DSM-5(4); DSM-5(4), Diagnostic and Statistical Manual of Mental Disorders, 5th(4th) edition; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; IWRS, Interactive Web Randomization System; MDMA, 3,4-Methylenedioxymethamphetamine; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias; SAE, serious adverse events; SD, standard deviation; SDS, Sheehan Disability Scale; SOC, States of Consciousness questionnaire.

a. Based on primary blinded study period assessing primary outcome.

Table J1. Explanation for Risk of Bias Ratings for the Domain-based Risk of Bias Assessment

Study	Allocation sequence generation	Allocation sequence concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data (attrition)	Selective reporting	Total Jadad Score
	method used to generate the allocation sequence.	code from the web system for each participant corresponding to a masked container.	standardize psychotherapy, and were therefore unblinded. The remaining participants/personnel were blinded; there is insufficient information to assess this blinding success.	standardize psychotherapy, and were therefore unblinded. The remaining participants/personnel were blinded; there is insufficient information to assess this blinding success. Study personnel being aware of the first 2 participants' assignments might increase risk of guessing the treatment arm of all participants, if personnel were involved in treatment of both. (Of 3 therapist teams, 2 cared for the first 2 open-label participants per study protocol.)	reports they were blinded during the entire study period.	and described as "completers" of the overall pilot study.	outcomes reported. However, efficacy outcomes are reported as mean and standard deviations without any formal statistical comparison between groups. There is inconsistency in the reporting of safety outcomes; suicidal ideation was reported, but vital sign information was not reported.	
Ot'alora et al. 2018 *J Psychopharmacol* (NCT01793610) [46,52,58]	**Unclear**	**Low**	**High**	**High**	**Low**	**High**	**High**	Jadad score = 2[a]
	Jadad score = 1		Jadad score = 1[a]			Jadad score = 0		
	Allocation was performed by an "unblinded randomization monitor," but there was insufficient information about the method used to generate the allocation sequence.	From the protocol, it appears a web-based system was used to maintain randomization codes. Blinded personnel received an enrollment code from the web system for each participant corresponding to a masked container.	Participants were blinded to their allocation; however, when asked after each experimental dosing session to guess which group they were assigned, "Participants also guessed correctly often, 72.7% in the 40 mg sessions, but mistakenly guessed (41.9%) a low dose when in fact they had received an active dose."[46]	Therapists were blinded to their allocation; however, when asked after each experimental dosing session to guess which group the participant was assigned, they correctly guessed 86% of the time for the experimental sessions (100mg and 125 mg), and 77% of the time for the comparator sessions.	Blinded outcome assessors that were not exposed to participants' therapy sessions (eg, including vital sign data, which may increase the risk of unblinding) assessed the primary efficacy outcome measure (CAPS-4)	Overall attrition was 7% (2 of 28 participants withdrew from the study: 1 from the comparator arm due to achieving early efficacy after 1 dose, and the other from the experimental arm for unknown reasons). The participant that withdrew due to efficacy was included in the ITT analysis, but the participant that withdrew for unknown reasons (representing 7.8% of the MDMA 125 mg arm) was not. Overall, 5 of 28 enrolled participants (17.9%) were missing from the PP analysis. (Three additional participants from the MDMA 125 mg arm revealed exclusionary psychiatric diagnoses during treatment and were excluded from the PP but not ITT analysis.)	Comparing information reported in the publication to ClinicalTrials.gov and the study protocol yielded a minor discrepancy between the published article and ClinicalTrials.gov in the number of participants included in the primary outcome analysis: 13 per ClinicalTrials.gov, vs 12 per article in the ITT analysis for the MDMA 125 mg arm. There are also discrepancies in outcomes in the study protocol vs what is reported on ClinicalTrials.gov and in the publication. The study protocol indicated the collection of participant-reported PTSD symptoms using the PDS, GAF, and PTGI, but these are not reported by either ClinicalTrials.gov or the article.	

Abbreviations: AE, adverse event; CAPS-5(4), Clinician-administered PTSD Scale for DSM-5(4); DSM-5(4), Diagnostic and Statistical Manual of Mental Disorders, 5th(4th) edition; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; IWRS, Interactive Web Randomization System; MDMA, 3,4-Methylenedioxymethamphetamine; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias; SAE, serious adverse events; SD, standard deviation; SDS, Sheehan Disability Scale; SOC, States of Consciousness questionnaire.

a. Based on primary blinded study period assessing primary outcome.

Table J1. Explanation for Risk of Bias Ratings for the Domain-based Risk of Bias Assessment

Study	Allocation sequence generation	Allocation sequence concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data (attrition)	Selective reporting	Total Jadad Score
Mithoefer et al. 2018 *Lancet Psychiat* (NCT01211405) [47,53]	**Unclear**	**Low**	**High**	**High**	**Low**	**Unclear**	**High**	Jadad score = 3[a]
	Jadad score = 1		Jadad score = 1[a]			Jadad score = 1		
	Allocation was performed by an "unblinded Randomization Monitor" (also the person labelling and masking the containers for the study drugs), but there was insufficient information regarding the technique used to generate the allocation sequence.	A web-based system was used to store the randomization codes. The study protocol also mentions giving investigators "sealed emergency unblinding envelopes" that were stored in a secure area and only accessed in the event of an emergency. This procedure was likely adequate for allocation concealment.	Despite appropriate blinding, participants were able to correctly guess their treatment arm 46.3% of the time. To be counted as a correct guess, participants needed to guess the exact dose (ie, 30 mg, 75 mg, or 125 mg), not merely whether they were in the comparator or experimental arms. Most incorrect doses were due to failing to distinguish between the active MDMA arms (ie, MDMA 75 or 125 mg).	Despite appropriate blinding, therapists were able to correctly guess the participant treatment arm 57-59% of the time. To be counted as a correct guess, therapists needed to guess the exact dose (ie, 30 mg, 75 mg, or 125 mg), not merely whether participants were in the comparator or experimental arms. Most incorrect doses were due to failing to distinguish between the active MDMA arms (ie, MDMA 75 or 125 mg).	Blinded outcome assessors that were not exposed to participants' therapy sessions (eg, including vital sign data, which may increase the risk of unblinding) assessed the primary efficacy outcome measure (CAPS-4).	Two participants (8%, 2 of 26 total) discontinued treatment after one experimental dosing session: 1 participant in the low-dose comparator arm (due to AE), and 1 participant in the mid-dose comparator arm (due to efficacy after 1 session). The article reports collecting primary outcome data from these participants, making this an ITT analysis. We nonetheless consider the ROB to be Unclear due to lack of detail regarding the AE in the low-dose comparator arm.	Comparing information reported in the publication to ClinicalTrials.gov and the study protocol yielded no discrepancies in the number of participants included in outcome assessments. One discrepancy in a planned, secondary outcome listed in the protocol but not in the article or ClinicalTrials.gov was identified: the States of Consciousness Questionnaire (SOC). Not reporting this outcome means High ROB, although this outcome may not have been important for measuring PTSD symptoms.	
Oehen et al. 2013 *J Psychopharmacol* (NCT00353938) [48,54]	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Low**	**High**	**High**	Jadad score = 3[a]
	Jadad score = 1		Jadad score = 1[a]			Jadad score = 1		
	Methods used for random sequence generation are unclear. The study is described as randomized, and allocation was performed by a separate party from the Department of Clinical Research. No study protocol was available for additional detail.	Information about concealment is insufficient. Investigators are described as blinded, and a separate party from the Department of Clinical Research performed randomization, but there is no information about storage/access to the agents and randomization codes. No study protocol was available for additional detail.	Participants are described as being blinded. Nonetheless, 4 of 8 participants (50%) in the experimental arm correctly guessed their treatment arm, while 1 was uncertain and 2 were incorrect. Two of five participants (40%) in the comparator arm guessed correctly, with another 2 being incorrect and 1 uncertain. When personnel and participant guesses were combined, 59% of guesses were correct (66% for experimental arm, and 46% for comparator arm) and 41% incorrect. Authors of the article concluded this overall guess-rate was close enough to chance, and that blinding was generally successful.	Personnel are described as being blinded. Nonetheless, 8 of 9 investigators overseeing an experimental arm (88.8%) correctly guessed the treatment arm, while 1 was uncertain. In the comparator arm, 2 of 5 investigators (40%) guessed correctly, while 1 guessed incorrectly and 2 were uncertain. When personnel and participant guesses were combined, 59% of guesses were correct (66% for experimental arm, and 46% for comparator arm) and 41% incorrect. Authors of the article concluded this overall guess-rate was close enough to chance, and that blinding was generally successful.	All outcomes were measured by a blinded "independent rater." They describe breaking the blind after the last independent rater measurement of the primary outcome.	The type of analysis (eg, ITT or PP) is not specified. However, of 14 participants randomized (9 to active MDMA and 5 to active placebo), 12 were included in the analysis of primary outcome. The 2 missing participants (1 from each study arm) were described as withdrawing after 1 experimental dosing session due to AE. We did not find any additional information about the nature of these AEs.	Comparing information reported in the publication to ClinicalTrials.gov yielded a discrepancy in the number of comparator-arm participants completing the trial. The published article states 4 of 5 completed; ClinicalTrials.gov reports 5 of 5 completed, while giving efficacy outcomes for only 4 participants. Additionally, ClinicalTrials.gov reports 2 SAEs occurred in the experimental arm (1 being suicidal behavior); however, the article appears to interpret these SAEs as not drug-related. No protocol was available.	

Abbreviations: AE, adverse event; CAPS-5(4), Clinician-administered PTSD Scale for DSM-5(4); DSM-5(4), Diagnostic and Statistical Manual of Mental Disorders, 5th(4th) edition; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; IWRS, Interactive Web Randomization System; MDMA, 3,4-Methylenedioxymethamphetamine; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias; SAE, serious adverse events; SD, standard deviation; SDS, Sheehan Disability Scale; SOC, States of Consciousness questionnaire.

a. Based on primary blinded study period assessing primary outcome.

Table J1. Explanation for Risk of Bias Ratings for the Domain-based Risk of Bias Assessment

Study	Allocation sequence generation	Allocation sequence concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data (attrition)	Selective reporting	Total Jadad Score
Mithoefer et al. 2011 *J Psychopharmacol* (NCT00090064) [49,55]	**Low**	**Unclear**	**High**	**High**	**Low**	**High**	**High**	Jadad score = 3
	Jadad score = 2		Jadad score = 1			Jadad score = 0		
	Study described as randomized, and randomization was determined by a computer-generated allocation sequence.	The published study reports use of an "independent randomization monitor" who assigned and distributed bottles containing agents. More detail is needed to determine adequacy of concealment. Notably, no mention of a randomization monitor is mentioned in the study protocol.	Despite assurances of blinding, 95% (19 of 20) of the participants analyzed for primary outcome correctly guessed their treatment arm, with 3 of the 20 being slightly uncertain of their final guess. The study used an inactive placebo, which was undoubtedly a factor in the failure of the blinding.	Therapists guess correctly for all participants' treatment arms, although 3 therapists were slightly uncertain of their final guess. The study used an inactive placebo, which was undoubtedly a factor in the failure of the blinding.	Blinded independent raters, who were not present during treatment sessions, assessed study efficacy outcomes.	The analysis population was PP only: 3 of 15 experimental arm participants (20%) dropped out (1 depression relapse, 1 unwilling to travel, and 1 not having treatment-resistant PTSD), and 0 of 8 comparator participants (0%) dropped out. ROB is considered High due to the differential rate of attrition between arms, and missing outcomes not being in the analysis.	Comparing information reported in the publication to ClinicalTrials.gov yielded no discrepancies in the number of participants randomized or the number analyzed for primary outcome. There are minor discrepancies in the values reported for the primary outcome at the primary endpoint (eg, SD on ClinicalTrials.gov is 25 vs 8 in published article). Also, although ClinicalTrials.gov reports 2 SAEs, the published article does not mention them, considering them not drug-related.	
Unpublished report ClinicalTrials.gov (NCT00402298) [43]	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**High**	**Unclear**	Jadad score = 2[a]
	Jadad score = 1		Jadad score = 1[a]			Jadad score = 0		
	Described as "randomized" on ClinicalTrials.gov, but there is insufficient information to assess the randomization method. No study protocol was available.	No information to assess method of allocation concealment was available.	Participants are described as blinded during the blinded portion of the study assessing primary outcome; however, there is insufficient information to assess blinding success.	Personnel are described as blinded during the blinded portion of the study assessing primary outcome; however, there is insufficient information to assess blinding success.	Outcomes assessors are described as blinded, but owing to the lack of study protocol, there is insufficient information for verification.	Of 3 participants in the experimental arm, 1 withdrew; 0 of 2 participants in the comparator arm withdrew. Overall attrition rate of the small number of participants was 20%. No further reason for withdrawal was given. Data for this participant was not included in the primary outcome analysis.	There is no published protocol, so there is insufficient information for assessment.	

Abbreviations: AE, adverse event; CAPS-5(4), Clinician-administered PTSD Scale for DSM-5(4); DSM-5(4), Diagnostic and Statistical Manual of Mental Disorders, 5th(4th) edition; GAF, Global Assessment of Functioning; (m)ITT, (modified) intent-to-treat; IWRS, Interactive Web Randomization System; MDMA, 3,4-Methylenedioxymethamphetamine; PDS, Post-traumatic Diagnostic Scale; PP, per-protocol; PTGI, Post-traumatic Growth Inventory; PTSD, post-traumatic stress disorder; ROB, risk of bias; SAE, serious adverse events; SD, standard deviation; SDS, Sheehan Disability Scale; SOC, States of Consciousness questionnaire.

a. Based on primary blinded study period assessing primary outcome.

Table J2. Supplemental Risk of Bias Assessment

Study	Adherence		Funding Bias		Other Notes
	Adherence to MDMA and Psychotherapy	Re-training of Therapists	Study Sponsor	Sponsor's Role	
Mitchell et al 2021 (NCT03537014) [32,50,60]	Administration of interventional drugs was observed by clinicians, and protocol deviations address issues of non-adherence. Participant completion of experimental dosing sessions is reported as 42 of 46 (91%) completing all 3 MDMA sessions, and 37 of 44 (84%) completed all 3 placebo sessions.	Fidelity of the therapist dyads to the planned psychotherapy protocol was not reported, despite the protocol stating that independent "adherence raters" assessed fidelity according to a rating tool. Inclusion of "re-training" was not reported (only initial training).	Funded by the non-profit organization, MAPS, using privately donated funds.	MAPS was involved in the study design, study monitoring, analysis and interpretation of data, and review of the publication. They were not involved in data collection or study conduct. Approximately 7 authors of the publication were MAPS employees or have been employed by MAPS in the past. Most of the other authors of the report received funding from MAPS to conduct this study and possibly other prior studies.	Participant demographics are relatively balanced between arms. One potential difference that could favor greater effectiveness in the MDMA group is that 6 participants in the MDMA arm (vs 13 participants in the placebo arm) were considered to have the harder-to-treat, "dissociative" subtype of PTSD. The investigators reported the effect sizes for each treatment arm as similar for those with or without the dissociative subtype. In an analysis of covariates, only the dissociative subtype was shown to significantly impact the primary efficacy result, and also to significantly interact with the treatment group. It is not clear, but it seems like the size of the MDMA effect is slightly larger for the dissociative subtype group vs non-dissociative subtype, suggesting the interaction with treatment group favors MDMA vs placebo.
Unpublished ClinicalTrials.gov report (NCT01958593) [44,59]	There is insufficient information to assess adherence. ClinicalTrials.gov included all enrolled participants in the analysis, but did not include explicit mention of adherence.	Plans for training and adherence to the psychotherapy protocol were defined and well-prepared (from protocol), but outcomes of this are not reported. There was no information about re-training of therapists.	Funded by the non-profit organization, MAPS.	At a minimum, the study protocol describes MAPS involvement in study monitoring, analysis, and interpretation of data. A MAPS employee reported results on ClinicalTrials.gov.	
Unpublished ClinicalTrials.gov report (NCT01689740) [45,51]	There is insufficient information to assess adherence. ClinicalTrials.gov included all enrolled participants in the analysis and described all 10 participants as "completers," but did not include explicit mention of adherence.	The study included an open-label, lead-in phase of 2 participants and 2 therapist dyads to assist with training of the therapists and standardization of the psychotherapy protocol (including feedback on their psychotherapeutic approach; per study protocol, this would be given to 2 of 3 therapy teams). No additional information about re-training was available.	Funded by the non-profit organization, MAPS.	At a minimum, the study protocol describes MAPS involvement in monitoring psychotherapy in the open-label, lead-in phase, additional study monitoring, and data analysis.	
Ot'alora 2018 (NCT01793610)[46,52,58]	"Adherence" is not specifically described, but they report that 2 participants withdrew from the study (1 in the low-dose comparator arm after only 1 dosing session, and the other from the high-dose experimental arm after an unknown number of doses).	Plans for training and adherence to the psychotherapy protocol were defined and well-prepared (from protocol), but outcomes of this are not reported. (They recorded therapy sessions and used independent adherence raters to assess fidelity to the therapy protocol.) There was no information about re-training of therapists.	Funded by the non-profit organization, MAPS.	Six of 12 study authors were MAPS employees. At least some of these MAPS employee authors were involved in the study design, data collection, analysis and interpretation of data, and drafting of the manuscript. The majority of additional authors declared receiving funding from MAPS for their role on this project.	Investigators report "This is the first trial to employ multiple therapy teams with newly trained therapists implementing the manualized approach." [46]
Mithoefer 2018 (NCT01211405)[47,53]	"Adherence" is not specifically described, but they report that 2 participants withdrew from the study after completing only 1 of 2 experimental dosing sessions (1 participant in	Plans for training and adherence to the psychotherapy protocol were defined and well-prepared (from protocol), but outcomes of this are not reported. (They recorded therapy	Funded by the non-profit organization, MAPS.	The sponsor was involved in various trial activities, including design, data monitoring, data interpretation, and preparation of the manuscript. The sponsor was not involved in data collection/conduct. Five of 11 authors	Study protocol describes the goal of using adherence raters as follows: "The goal of these ratings will be to correlate therapist adherence to the Treatment Manual with outcome as part of the sponsor's ongoing efforts to

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	the low-dose comparator arm, and 1 participant in the high-dose experimental arm).	sessions and used independent adherence raters to assess fidelity to the therapy.) There was no information about re-training of therapists.		of the study are MAPS employees, and most of the others declared receiving funding from MAPS. Only 1 author declared no competing interests.	standardize treatment methods of MDMA-assisted psychotherapy for PTSD."[57]
Oehen 2013 (NCT00353938)[48,54]	"Adherence" is not specifically described. They report that 2 of 14 participants withdrew from the study after the first experimental session (1 from each study arm).	According to the publication, therapists followed a protocol, and adherence raters assessed fidelity to the protocol. Based on a post-hoc assessment, the investigators report that in some cases therapists deviated from the therapy protocol (eg, too directive instead of non-directive), but there are no additional details on this.	Funded by MAPS and by the Swiss Medical Association for Psycholytic Therapy (SAePT).	MAPS had a role in the study design and study monitoring. The first author is on the Board of Directors of SAePT. Three of four article authors received funding from the sponsors to conduct/play a role in the study.	
Mithoefer 2011 (NCT00090064)[49,55]	"Adherence" is not specifically described, but 3 participants from the experimental arm withdrew from the study, including 2 participants that "dropped out before the second experimental session," and 1 who perhaps did not complete any sessions, as it was later confirmed they did not meet inclusion criteria.	Fidelity of the therapist dyads to the planned psychotherapy approach was not reported. Investigators specifically note this as a limitation of the study: "The absence of therapist adherence measures was an unavoidable weakness of this first pilot study."	Funded by the non-profit organization, MAPS.	"The sponsor played a role in study design, data analysis and writing of the report." Two investigators involved in data collection were disclosed as MAPS employees; the primary author is a medical monitor for other MAPS studies; and the primary author and two other others have received funding from MAPS.	
Unpublished ClinicalTrials.gov report (NCT00402298)[43]	There is insufficient information to assess adherence. ClinicalTrials.gov reports that 80% of participants were included in the primary efficacy analysis but does not include explicit mention of adherence.	No information reported.	Funded by the non-profit organization, MAPS.	Insufficient information to assess. ClinicalTrials.gov reports the principal investigators of the study were not employees of the sponsoring organization. Also, limited data were reported to the sponsor (relating to early termination), implying that the sponsor was at least involved in data monitoring.	Results from this study were not included among pooled analyses included in the qualitative summary. The study was terminated early due to staff turnover and an impact on the quality of data collected. The impact of this on information reported on ClinicalTrials.gov is unclear. Reporters of results on ClinicalTrials.gov state that the quality of data cannot be guaranteed.